Revealing Local Information

Identification of Salient Functional Brain Links in Resting State Brain

Pallabi Sengupta

TESI DOCTORAL UPF / ANY 2017

DIRECTOR DE LA TESI
Prof. Nuria Sebastian-Galles Departament Biomedicine

To all the women who made it possible for me to pursue an academic career

Acknowledgements

I would like to thank the grant that I received from the European Community's Seventh Framework Programme (FP7/2007-2013): ERG grant agreement number 323961 (Under Control). Now that this formality is over, I would like to thank Dr. Anna Basora and Dr. Hernando Sanatamaría-García, whose data-sets I used. Their theses and, published papers, along with their feedback on the manuscripts helped me a lot in this thesis. I would like to thank the secretariat of the CBC, especially Florenica Nava and Xavier Mayoral (Xavi). Florencia helped me a lot with bureaucracy and personal difficulties. Xavi was really helpful with computer issues.

I would also like to thank Dr. Miguel Burgaleta, Dr. Gorka Zamora López and, Prof. Gustavo Deco. I would like to give a special thanks to Prof. Nuria Sebasitian Galles, for accepting me as a PhD student. Both Miguel a.k.a Miguelinksi and, Gorka a.k.a Gorkus Maximus were the one of the best supervisors that one could ask for. They helped me so much during the thesis. I was able to learn a lot from the SAP and CNS groups especially during the group meetings. Therefore, I would also like to thank these two groups.

I would definitely like to thank my friends that I made here in Barcelona and the ones that I left back home. Some honorable mentions are Katharina, Adrian, Mohit, Cristina, Elisa, Camille, Marina, Joanna, Sara, Shanmukhi, Iñigo, Txema, Luis, Meri, Edina, Loreto, Nils and Gyan. My friedns here especially Elisa, Marina, Edina, Meri and, Irene made me feel like I have a family here. Their support were crucial for some of the most difficult times that I faced here. I would like to thank my husband Rikkert, who was so encouraging and supportive throughout my thesis. Finally, I would like to thank all the women who made it possible for me to pursue academia, especially my mother, Ratna Sengupta and my grandmother, Manju Sengupta. They raised me to be a strong independent feminist woman, which helped me a lot to stay strong at the face of discrimination and other hardships. I would also like to thank the Feminist Journal Club and the various guests whom we had, Prof. Virginia Valian and, Prof Ana Gonzalez. I would also like to thank Prof. Rebecca Jordan Young and my future supervisor Prof. Anelis Kaiser.

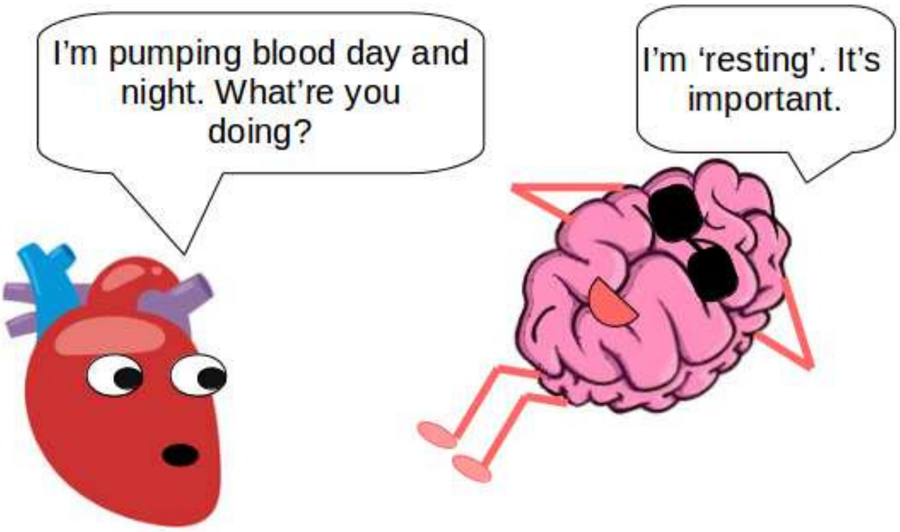
Abstract

Communication amongst various regions of our brain makes it possible for us to perform a wide array of cognitive tasks. To capture these communications at a local level has remained challenging in the field of neuromaging due to the sheer number of functional brain links that is needed to be explored. Different methods aimed at investigating these links either focuses on selection biases or increases the complexity of the method. The current thesis addresses this issue, by introducing a new simple method, namely Link Wise Median Splitting, which remains free of any selection biases. With the aid of simulations, we first demonstrated the higher sensitivity of this method over traditional approaches. Furthering the versatility of the method, we applied it to three different study designs involving resting state functional connectivity. The three study designs aimed to understand three distinct cognitive processes, revealed crucial information about the resting state brain. In sum, this thesis concluded by showing the benefits of using Link Wise Median Splitting over traditional methods to investigate functional brain links.

Resum

La comunicació entre diverses regions del nostre cervell fa possible que fem una àmplia gamma de tasques cognitives. Capturar aquestes comunicacions a nivell local és encara un repte en el camp de la neuroimatge degut a la gran quantitat de connexions cerebrals funcionals que cal explorar. Els diferents mètodes destinats a investigar aquestes connexions es centren o bé en els biaixos de selecció o bé en augmentar la complexitat del mètode. La tesi actual aborda aquest assumpte introduint un nou mètode senzill, l'anomenat Link Wise Median Splitting, que queda lliure de biaixos de selecció . Amb l'ajuda de simulacions, primer hem demostrat la major sensibilitat d'aquest mètode respecte als enfocaments tradicionals. Aprofundint en la versatilitat del mètode, l'hem aplicat a tres dissenys d'estudi diferents de connectivitat funcional en l'estat de repòs. Els tres dissenys d'estudi, adreçats a comprendre tres processos cognitius diferents, han revelat informació crucial sobre el cervell en l'estat de repòs. En resum, aquesta tesi mostra els beneficis de l'ús de Link Wise Median Splitting sobre mètodes tradicionals per investigar connexions funcionals del cervell.

Preface



According to an old English proverb 'An idle brain is the devil's workshop'. Indeed there is some truth to this proverb. Scientifically, no experiment can prove or disprove whether the workshop, that is in our brain can be devilish or not. However, the existence of a 'workshop' which is constantly active even during 'rest', has been shown in the previous decades. Biologically speaking, this finding is mind-boggling because not only does the brain consume a large amount of energy, relative to its mass but also the amount of energy consumed when we are idle, is rather high. The only explanation for such high consumption is the need of a baseline which is required to perform different cognitive tasks. In support of this view, Smith and colleagues [Smith et al., 2009] have shown a high correlation between the 'task' state and idle or 'resting' state of the brain. In fact resting state studies have now boomed in understanding of various disorders arising from the argument that the difference in baseline will cause differences observed in behavioral and cognitive deficits. Since subjects are not required to perform anything at all during the acquisition of resting state brain scans, we can finally learn about vegetative and coma patients, thanks to this phenomenon.

An important issue then, is the information obtained from the resting state scans at different levels. At a global level graph theoretical techniques are often used to understand the communication pattern between the different brain regions revealing crucial information. At a local level, researchers face various complications due the sheer number of brain connections or activation in brain regions leading to the problem of multiple comparisons. Different analysis methods work around this problem by choosing the regions of analysis prior to the analysis or clustering or pattern algorithms and then selecting the clusters that 'make sense'. Most of the methods, however suffer from a pre or post selection bias as elaborated in the Introduction. The rest of the methods which reduce the extent of selection bias do so at the cost of increasing the complexity, making it difficult to interpret the analysis results. The current thesis introduces a new method aimed to deal with these issues.

The Introduction talks in detail, the need of understanding the resting state at a local method and the problems faced by different analysis methods. Chapter 2 introduces the method called Link Wise Median Split and compare its performance with traditional non-parametric methods with the aid of various simulations. We show that Link Wise Median Split increases the sensitivity and therefore the chance of detecting salient changes. The chapter ends with an applicability of LWA on a case-control data previously used to distinguish between rest and natural viewing conditions. LWA as opposed to non-parametric analysis detected three brain links encompassing visual, auditory and attention regions.

Chapters 3 and 4 are two more applications of Link Wise Median Split encompassing different study designs. These applications are primarily aimed to exhibit the versatility of Link Wise Median Split. In Chapter 3 participants are divided into groups randomly. Each participant either listened to an artificial language audio stream consisting of statistical regularities or a random audio stream devoid of any statistical pattern. We acquired resting state scans and the aim was to compare the changes in the resting state scan after subjects listened to the stimuli while controlling for their baseline activity. Using Link Wise Median Split we detected functional brain link between left Superior Parietal Lobe and right Posterior Cingulate Cortex which was significantly different between artificial language and control conditions showing the effect of attention and working memory in learning statistical regularities in auditory stream.

Chapter 4 shows the utilization in a study design devoid of case-control scenario showing the versatility of Link Wise Median Split. For this study, participants performed a social task used previously to test social hierarchy perception. We used a combination of Event Related Potential along with resting state functional neuroimaging to determine resting state neural correlates responsible for social hierarchy perception. Using Link Wise Median Split we detected two functional brain links, right Insula – left Parahippocampal Gyrus, and left Superior Frontal Medial – left Superior Temporal Sulcus which correlated with social hierarchy perception across all subjects. In the end, the Discussion ties all the results together and includes future directions of this work.

Summary

List of Figures

List of Tables

Chapter 1

INTRODUCTION

1.1 General Overview: Resting State Brain

Our brain is the most wonderful organ of our body. It is constantly active and consumes a large percentage of energy. In fact, even though the brain only amounts to 2% of the body weight, it consumes 20% of the oxygen [Clarke and Sokoloff, 1999]. This could only arise from an extremely high metabolic rate owing to its high energy requirement. Surprisingly, a large part of this energy is consumed during 'rest', when we are doing nothing. On the other hand, only 5% - 10% of this energy is consumed during cognitive tasks, even during most vigorous perceptual and motor activities [Raichle and Mintun, 2006]. It is attractive to assume that the high amount of energy consumed during rest must be used for maintenance purposes because what can the brain possibly be doing! Surely, it cannot be firing its neurons because what would be the purpose of that? But it has been shown that indeed up to 80% of the entire energy consumption of the brain at rest is for neural processes [Shulman et al., 2004].

This brings us to the idea of 'resting state brain', a concept introduced by [Biswal et al., 1995]. They showed that the correlation patterns between brain voxels activated during a simple finger tapping task is very similar to the correlation pattern of the same voxels during 'rest'. They found this pattern even for voxels located anatomically in different hemispheres. They claimed that the oscillations they found under 0.1 Hz must be of neural origin. [Smith et al., 2009], extended this finding by showing that the networks obtained from 'resting state brain' are quite similar to that of a wide repertoire of tasks. Several other studies have also confirmed these claims [Britz et al., 2010, de Pasquale et al., 2010]. This concept revolutionized functional neuroimaging, as evidenced by high number of studies published every year with 'resting state fMRI' as one of the keywords.

So what exactly is ’resting state’ and how much do we really know about it? As of now, the underlying reason for its existence is unknown [Biswal, 2012]. But we do know that the ’resting state’ consists of sets of brain regions that activate and deactivate together. These sets are called Resting State Networks (RSNs) where each network is thought to be responsible for certain cognitive tasks. This idea arises from the fact that often only one of the RSNs is activated during certain ’tasks’, while the others remain deactivated. This keeps the communication pattern amidst the RSNs similar even during ’tasks’ [Cole et al., 2014]. This phenomenon has made it possible to identify networks that are activated during certain tasks without making the subjects perform them [Cordes et al., 2002, De Luca et al., 2005]. This feature of RSNs has been exploited to determine the potential biomarkers of various disorders removing possible confounds arising from the task performance.

For example, if a study is aimed to explore the neural correlates of Parkinson’s disease, specifically the correlates responsible for slowness of movement, the difference of performance during motor tasks will not lead to possible confounds in the study. If one cannot perform the task as well as the control group, how can their neural activity be possibly compared? Correlating just the difference of performance of the two groups with the differences of neural activity can never rule out the possible confound of individual differences in the performance. Sure, one can argue that if the estimation of performance is done on proper sample population, individual variation hardly possesses any risk. However, gathering high number of patients and controls for proper estimation remains a challenge in the field of neuroimaging. Thankfully, this problem is now solved with the help of RSNs. Now researchers can just observe the differences in the activity of the RSN(s) responsible for motor task.

This makes the identification of RSNs responsible for motor as well as other tasks extremely important. This also makes one think of RSNs as stable networks making their numbers in our brain constant for all individuals. Any change in any aspect of these RSNs therefore, could be predicted as the presence of a disorder. Interestingly though, the sets of regions for each RSNs and therefore, the number of RSNs vary in the range of 6-10 depending on the method used [Damoiseaux et al., 2008, Beckmann et al., 2005]. The most prominent ones are: Default Mode Network (DMN), left and right Executive Control Network (ECN), Salience Network (SAL), Sensorimotor Network (SMN), Auditory, and Visual networks (Figure 1.1).

The DMN, which is the one of the most widely studied RSN, was discovered

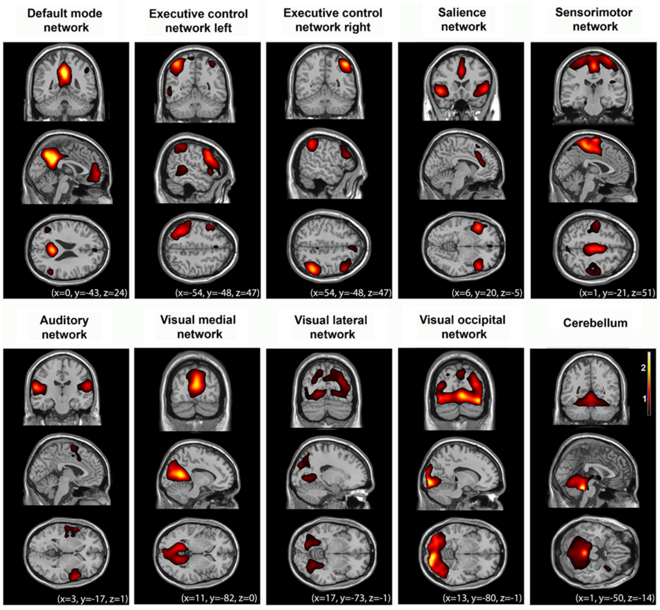


Figure 1.1: Resting State Networks as shown in [Heine et al., 2012]

by [Raichle et al., 2001]. They showed that a set a regions decrease its activation in light of attention-oriented tasks. The DMN roughly consists of ’core’ regions and two distinct sub-systems [Yeo et al., 2011]. Core regions are anterior medial Prefrontal Cortex (amPFC), Posterior Cingulate Cortex (PCC), bilateral Angular Gyrus (AG), lateral Temporal Lobes, and Superior Frontal Gyrus (SFG). The two subsystems are ’dorsomedial subsystem’ and ’medial temporal subsystem’. Dorsomedial subsystem comprises of dorsal medial Prefrontal Cortex (dmPFC), Temporo-Parietal Junction (TPJ), lateral Temporal Cortex, Temporal Pole, and Inferior Frontal Gyrus (IFG).

The dorsomedial subsystem has been constantly implicated in mentalizing, which refers to the cognitive process of inferring thoughts, beliefs, etc., of others [Mar, 2011, Schilbach et al., 2008]. The medial temporal subsystem on the other hand, has been implicated in mental simulation and imagination [Andrews-Hanna, 2012]. The ’core’ regions are implicated in a wide array of cognitive processes, but the most common ones are ’self-related’ tasks [Brewer et al., 2013, D’Argembeau, 2013]. This makes one think that DMN must be responsible for thinking about ’self’, which is an essential step for social processes. This thought has been previously voiced by [Mars et al., 2012] who showed that there is a major overlap between the DMN and the brain regions involved in social cognition.

The ECN comprises of dorsolateral Prefrontal Cortex (dlPFC), bilateral Inferior Parietal Lobes (IPL), Anterior Cingulate Cortex (ACC) or Supplementary Motor Area (SMA), and bilateral Insular Cortices. The left part of the ECN is involved with language tasks while the right side is implicated in perceptual, somesthetic, and nociception processing [Laird et al., 2011]. The ECN arguably hosts the most versatile regions of the brain, i.e., all the region of ECN are involved in a multitude of tasks ranging from decision making to reading to even pain perception [Krawczyk, 2002, Henseler et al., 2014, Uddin, 2014, Simons et al., 2014]. The one common feature of all these tasks is that they are mostly higher order cognitive processes. Owing to this feature, the ECN is thought to be the 'goal-directed' network [Littow et al., 2015].

The SAL network comprises of frontoinsular areas and ACCs along with connections to subcortical and limbic structures. The subcortical areas consist of the amygdala, ventral striatum, and ventral tegmental area, which are implicated in context-specific access to affective and reward cues [Lindquist et al., 2012](Lindquist et al., 2012; Menon, 2015). It shares its regions with the DMN and ECN making it act like a bridge between them [Menon and Uddin, 2010]. This makes it possible for our brains to switch between task state and resting state. It has also been implicated in orientation towards salient emotional stimuli, conflict monitoring, information integration, acute pain perception, and response selection [Cole and Schneider, 2007, Roberts and Hall, 2008, Tracey and Mantyh, 2007, Seeley et al., 2007].

The SMN hosts the original activations observed by Biswal et al., 1995. It consists of midcingulate cortex/SMA, bilateral Primary Motor Cortex (PMC), and bilateral Middle Frontal Gyri (MFG). The SMN is largely associated with motion and sensory processes related to motion. In fact, the activations in SMN have been observed even before occurrence of a movement or when the subjects were shown an object that can be grasped [Nachev et al., 2008, Grèzes and Decety, 2002]. The PMC, a major hub of SMN, is said to contain the muscular map of the body where the head is represented laterally, the leg is represented medially and the rest by intermediate locations [Colby, 2009].

Both Auditory and Visual Networks as their names suggest, are activated during auditory and visual tasks, respectively. The Auditory Network not only plays a role in classic auditory tasks like tone/pitch discrimination or music but also for speech [Laird et al., 2011]. This shows that the Auditory Network is also responsible for higher order cognitive processes which go beyond the auditory modality. The Auditory Network encompasses primary and secondary auditory cortices, including Heschl's Gyrus (HG), bilateral Superior Temporal Gyri (STG), and posterior Insular Cortex. Similar to the PMC, the primary auditory cortex possesses topographical map of the cochlea, which is the sensory epithelia in the auditory modality [Winer and Schreiner, 2009].

The Visual Network can be subdivided into lateral, medial and occipital parts. The lateral and medial parts of the Visual Network are responsible for simple visual processing while the occipital part is implicated in higher order visual processing [Damoiseaux et al., 2006, Castellazzi et al., 2014]. The area that is often not associated with any RSN is the Cerebellum. Even though it is sometimes linked with the Auditory Network, its function sets it apart [Castellazzi et al., 2014]. It was thought to only play a role in planning and execution of movements [Buckner, 2013]. However, recent findings have changed this perspective by showing its role in a wide range of cognitive tasks like single word-processing [Petersen et al., 1998], completion of a puzzle [Kim et al., 1994], among others [Buckner, 2013].

It seems that these RSNs are clearly defined separate faculties of the brain, only activating when specific functions are needed to be performed. Even though, we have stopped thinking about one-to-one mapping of brain regions we still think of RSNs as departments which perform similar set of functions. For example, DMN is often associated with mentalizing and self-related tasks while SMN is only associated with movements. This tendency can be traced back to Broca himself, who wanted to find evidence of language localization and discovered Broca'area [Berker, 1986]. More than a century later, Broca's area is still largely associated only with language, even though it has been implicated for domain general mechanisms like working memory [Santi and Grodzinsky, 2007]. A similar tendency can also be observed with RSNs, where we think of them as stable departments which perform their designated functions.

We think of these departments to consist of exactly the same regions in different studies, even though it is clearly not the case. An example is that of ECN, which along with the Dorsal Attention Network (DAN) is referred as Central Executive Network (CEN) [Littow et al., 2015].The DAN consists of Intraparietal Sulcus (IPS)/Superior Parietal Lobule (SPL), frontal eye fields, and extrastriate visual areas. The reason why these are paired together is the similarity of the goal-oriented tasks performed by them. But depending on the study, these terms are used interchangeably [Littow et al., 2015].

It is important to remember that these RSNs often communicate between each other for normal functioning instead of just increasing/decreasing their activation as suggested by. This exhibits that instead of a one-to-one mapping of different cognitive functions on different brain areas, it is much more likely that multiple areas communicate between each other for a single task. Hence, we should look for functional connections instead of just the areas that are activated. One of the most prominent of these connections, that received considerable attention, is the 'anti-correlation' between DMN and the DAN (Figure 1.2). This relationship has been questioned by [Murphy et al., 2009], who showed that regressing out the global signal, which is one of the preprocessing steps in fMRI, will automatically induce anti-correlations. Even though, [Fox et al., 2013], demonstrated the presence of anticorrelations without this step, the situation remains unsolved and depends on the method of analysis [Murphy and Fox, 2017].

Several other important functional connections have been observed by acquiring two resting-state scans, before and after certain stimuli, and then comparing them. One such study has shown the alteration of functional connection between the visual cortex and SPL by "life kinetik" training [Demirakca et al., 2016]. Similarly, training of a novel visual discrimination task has been shown to alter the functional connection between visual cortex and anterior Insula [Baldassarre et al., 2012]. A simple button pressing task has been shown to induce changes in resting state functional connection between left and right motor cortices [Tung et al., 2013]. [Gordon et al., 2014] in a similar fashion, exhibited changes in the connection between DMN and SAL Network induced by working memory task. Taken together these studies show that the functional connections between two brain regions can be changed by certain tasks, which points to the fact that these functional connections must be needed to perform these tasks. This highlights the importance of understanding the role of functional connections to understand neural mechanisms underlying different cognitive processes.

1.2 Resting State Functional Connectivity

We can clearly see that there is enough evidence to show the importance of functional connections in cognitive tasks and resting state scans can be used to understand these connections. Another set of compelling evidence comes from exploring the functional connections in patients suffering from disorders. Of particular interest are 'dysconnectivities', i.e., functional connections during rest that are different in a group suffering from a particular disorder compared to that of healthy individuals. Apart from giving possible insight about a particular functional connection, understanding these dysconnectivities also give us a unique window to identify the possible causes of the disorders themselves. One can argue that func-

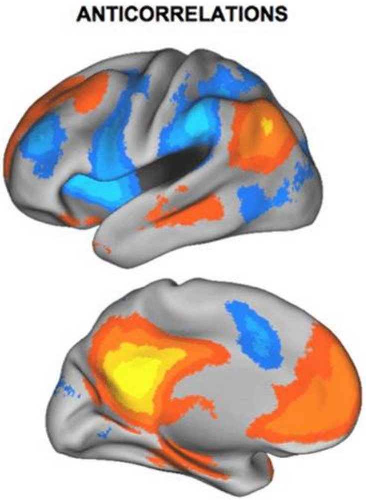


Figure 1.2: Anti-correlations observed between DMN and the DAN/ECN. The regions that are negatively correlated with the DMN are shown in blue and those that are positively correlated are shown in red. Used from [Buckner et al., 2009]

tional dysconnectivities can always be estimated using anatomical information. But, not all functional dysconnetions arise from altered anatomical connections, as is the case with Schizophrenia [Friston, 1998]. This makes observing the resting state dysconnectivities very special. These dysconnectivities can be categorized into two types, hyperconnectivity, i.e., higher connectivity between two brain regions as compared to that of normal individuals, and hypoconnectivity, i.e., lower connectivity.

Both hyper- and hypoconnectivity are observed in Alzheimer's patients and patients suffering from Mild Cognitive Impairment (MCI). Hypoconnectivity between left and right hippocampus, while hyperconnectivity in the SAL network have been shown in Alzheimer's and MCI patients [Li et al., 2002, Badhwar et al., 2017]. Hypoconnectivity in dorsal ACC (dACC) and hyperconnectivity in DMN areas have been consistently observed in depressed individuals [Anand et al., 2005, Greicius et al., 2007]. A key region of dysconnectivity in the DMN is the PFC showing both hypoconnectivty and hyperconnectivity with other brain regions in depressed cohorts [Mulders et al., 2015]. Combining depression with other dysfunctions like TBI (Traumatic Brain Injury) has shown the importance of functional connection between amygdala and SAL network as well as with CEN [Han et al., 2015].

Studies published in the previous decade have provided conflicting evidence regarding functional connections in Schizophrenia [Greicius, 2008]. Recent studies have shown hypoconnectivity between dlPFC and temporal regions and hyperconnectivity in the PFC in patients affected by Schizophrenia [Mingoia et al., 2012]. [Ćurčić-Blake et al., 2015] found increased connectivity from several DMN areas but lower white matter integrity in anatomical connections pointing to a possible reason of conflicting evidences found before. Another reason was determined by [Whitfield-Gabrieli et al., 2009] who showed toggle between DMN and TPN regions in not only schizophrenic patients but also in patients suffering from schizoaffective and schizophreniform disorder along with their first-degree relatives.

Autism is marked consistently by hypoconnectivity in the DMN [Jung et al., 2014, Murdaugh et al., 2012, Hull et al., 2017]. One prominent example of hypoconnectivity in Autism is between amygdala of the SAL network [Ypma et al., 2016]. Hypoconnectivity in DMN has been reported both for Attention Deficit Hyperactivity Disorder (ADHD) and ageing, pointing towards the domain general role of DMN [Castellanos et al., 2008, Damoiseaux et al., 2008].

Taken together, these studies highlight possible roles of the functional connections mentioned above. However, one has to remember that usually a disorder comprises of multiple symptoms and multiple dyconnectivities. Hence, it is more difficult to infer whether a functional connection is responsible for all the symptoms or only one of the several symptoms. Consider for example the hypoconnectivity of DMN in patients suffering from Autism Spectrum Disorder (ASD). We know that ASD is marked with lower social skills. Therefore, one can presume that the hypoconnectivity of DMN must be responsible for altered social skills. This can be furthered by the fact that DMN is associated with mentalizing and social tasks, as mentioned in the section above. However, many individuals with ASD also show higher perception and attention skills [Plaisted Grant and Davis, 2009]. Now, a key feature of the DMN is deactivation during attention tasks. Adding this key information into the picture makes one ask whether dysconnectivity of DMN can only be associated with lower social skills or only for higher attention or for both. Since, anti-correlation between DMN and DAN is exhibited in healthy individuals and DAN is known for its role in attention, can we then rule out the possible effect of DAN or rather its dysconnectivities in ASD?

This again raises the issue of understanding the roles of functional connections rather than just looking into the activations and deactivations of different brain regions. From the studies mentioned above, about changes in the resting-state brain either in a pre-post paradigm or in disease-control paradigm, one can infer the importance of looking into the differences/changes in resting-state functional connectivity (rsFC). The power of resting-state to explore various paradigms due to its simplicity is undeniable. However, a major challenge for the researchers then is to analyze them properly. If the analysis is affected by biases, the results obtained will not give a complete picture. This may seem straightforward, but we will see in the next subsections that pre- or post-analysis biases are quite common. These are usually put in place owing to the various restrictions imposed by the complexity of the brain. To understand these restrictions and the various ways different methods go around them, we will first have to understand what functional connectivity is.

1.2.1 What exactly is FC?

Functional Connectivity (FC) has been defined as 'temporal dependence of neuronal activity patterns of anatomically separated brain regions' [van den Heuvel and Hulshoff Pol, 2010]. It is evident that there is an underlying assumption of inter-areal synchronization of the neuronal activity in this definition [Bastos and Schoffelen, 2015]. Another assumption is that we can capture this activity as neuronal oscillations either through invasive or non-invasive techniques. Regardless of the method of detection, once these oscillations are recorded, the studies face the challenge of characterizing the 'temporal dependence'. A recent review has identified 42 distinct methods [Wang et al., 2014] exhibiting the sheer number of choices the researchers usually have. Since this is not the primary focus of the thesis, I will talk about only the most prominent ones.

All the methods can be classified on the basis of two parameters: directionality and the presence/absence of a model. Directionality signifies the direction of the neuronal interaction that can be captured with the method and the other category signifies whether an underlying model has been used to calculate the FC. Just the combination of different possibilities arising from these parameters gives us four different methods, depicted in Figure 2.1. The simplest and the most used method is the Pearson's correlation coefficient which is a non-directed model-based method. This method only captures the linear interaction. It is now common to transform the correlation coefficient values with Fisherâs z transform to ensure normality [Fisher, 1995, Valencia et al., 2009]. A more general approach which captures non-linear interactions as well is mutual information [Kraskov et al., 2004].

Both of the methods assume that the FC obtained will be the same even if the time-series of the areas concerned are shuffled. However, in real data when one of the time-series is shifted with respect to the other, the correlation value changes. This can be captured with cross-correlation function which evidently is a function of time. This has been used successfully to capture dominant one-directional interactions and the time-delay at which they have largest influence [Usrey et al., 1998]. However, complications arise with bi-directional interactions which are the case for majority of brain connections. In the case of bi-directional interactions, cross-correlation function lack clear peaks and have significant effects at both positive and negative time-lags [Bastos and Schoffelen, 2015]. This problem can be solved by using Granger Causality, which evaluates the extent of which the past value of one time-series can predict the future value of another time-series [Granger, 1969]. A similar approach is to calculate 'Effective Connectivity' which has been defined as 'the influence that one neural system exerts over another, either at a synaptic or population level' [Friston, 2011].

Finally, there are also model-free approaches to calculate directed FC values. One such method is transfer entropy which is a generalized information-theoretic approach to study delayed (directed) interactions [Lindner et al., 2011]. Unlike Granger Causality it is capable of capturing non-linear interactions. However, because of its generalized nature, the results can become difficult to interpret. It can be attractive to use transfer entropy even at the cost of difficulty of interpretation, to capture all possible interactions. But, it has been shown that time-series are mostly Gaussian in nature and therefore non-linear interactions does not amount to more information than linear ones [Hlinka et al., 2011]. All the aforementioned methods are calculated in the time domain which fails to capture rhythmic neuronal interactions. To do this it is beneficial to calculate FC in frequency domain which can be done by the application of non-parametric (Fourier decomposition, wavelet analysis, or Hilbert transformation after bandpass filtering) or parametric techniques (autoregressive models) [Bastos and Schoffelen, 2015]. Neuronal interactions in the frequency domain can be captured by determining the consistency (or lack thereof) in phase differences of the oscillations of the time-series. This is due to the fact that a non-random distribution of phase differences is most likely the result of synchronization between two oscillating neural populations.

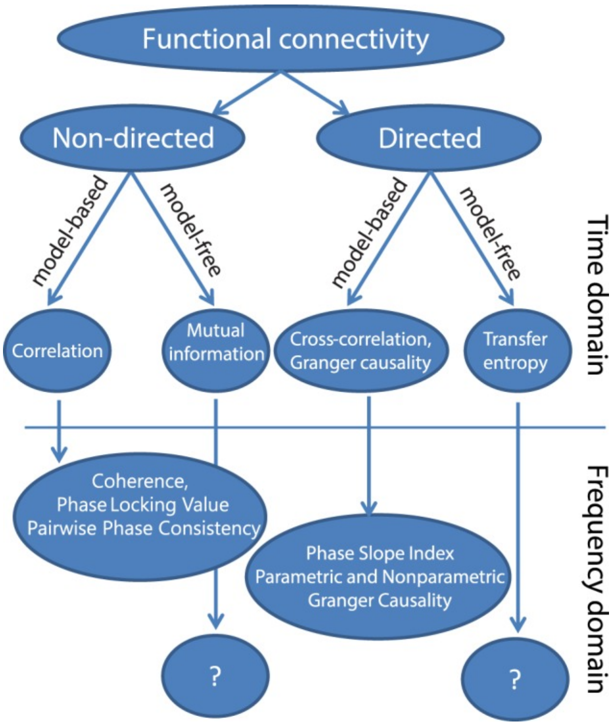


Figure 1.3: Most common methods to calculate FC. Image taken from [Bastos and Schoffelen, 2015]

The domain equivalent of Pearson's correlation coefficient in frequency domain is coherence coefficient. Its squared value denotes the extent to which the variance of one of the signals can be explained by the other, and vice-versa. Other methods include phase locking value, phase slope index, pairwise phase consistency and Granger Causality in frequency domain. There are also methods exploring the amplitude of the time-series which have been used successfully to quantify large-scale brain networks [Foster et al., 2015]. Since the current thesis focuses mainly on FC matrices calculated in the time domain, I will not go into the details of these methods.

1.2.2 FC Analyses

Just like calculation of FC, analyses on FCs can also be done with a large-array of methods. Here, I will only revisit the most used ones. In this section, I will assume that the FC matrices are calculated with Pearson's correlation coefficient since it is the most prevalent method used. However, all the methods listed below can be used on any kind of FC regardless of the way they are calculated. The methods can be broadly classified as 'local' or 'global' methods. Global methods look into the global topological properties of the resulting FC network while local methods focus into determining the significance of local interactions.

1.2.2.1 Graph Theory

This is one of the most common global methods used to characterize FC. Mathematically, the ability of considering each and every voxel/region as a **node** and the connections associated with the region to be **edge** makes it possible to explore FCs as graphs. An edge can be assigned between two nodes when the correlation coefficient is above a particular threshold value or they can be weighted. For these weighted and unweighted graphs, various graph theoretical parameters can be calculated. An important such parameter is the **path**, which is the sequence of edges that are connected and the minimum number of edges travelled to reach one node from the other is called **path-length** of the two nodes. Taking the average of all possible combinations of node pairs for a graph will give **average path length**, which gives information about the connectedness of the graph.

Another important parameter of the graph is the **degree** of a node, which signifies the number of edges the particular node possess. Just like average path length, **average degree** is the mean of degree across all nodes of the graph. This particular value gives an idea of how dense the graph is. But a better measure for that is the **density** of the graph, which is the proportion of existing connections divided by number of possible connections. Another parameter that can be calculated from the degree is the **degree distribution** of the graph which can tell us about the **hubs** of the graph. Hubs are usually nodes that are highly connected in the graph and are quite important as they bind various parts together. Using this concept Buckner and colleagues [Buckner et al., 2009], reported that brain areas with high 'hubness' deteriorate with higher probability in Alzheimer's Disease. **Eigenvector Centrality**, which uses a similar concept, has also been applied to analyze FC [Lohmann et al., 2010].

Degree distribution can also be used to test the **resiliency** of the graph. To perform such a test nodes of the graphs are 'attacked' by using either random error or targeted attack. In 'random error' a random node is repeatedly deleted from the graph, while 'target attack' repeatedly deletes the node with the actual highest degree. After each attack the vulnerability of the graph is measured by using various graph theoretical parameters. Using these approaches Achard and colleagues [Achard et al.,] showed that resting-state FC is more resilient than random scale-free graphs, while using random error but they perform equally bad with targeted attacks. An important parameter measuring local structure of the graph is **local**

clustering-coefficient which is the probability of an existing triangle given that there is a connection between two nodes via a third one. In other words it calculates the number of triangles when we know that the one of the nodes involved is definitely connected with the other two nodes. One can see that this can also be used to measure resiliency of the graph since removal of one of the edge will still ensure connectivity across all the three nodes. Using this measure combined with path-length [Rubinov et al., 2009] showed local and global differences in the resting-state FC of schizophrenic patients as compared to healthy individuals.

Modularity talks about how our brain is divided into different modules so that functions are segregated and are easier to perform. Using modularity measures [He et al., 2009], found that sensory and cognitive systems can be separated as modules which have sparse intermodule connections. Combining the two measures of modularity and hubness one can characterize the graph as a **small-world network**. Originally defined by Watts & Strogatz [Watts and Strogatz, 1999], a small-world network is a network with ideal balance between segregation and integration. Segregation in a network is required to compartmentalize the information while integration of the processing from these segregated 'departments' or modules, is required for proper functioning. Think of a small-world network as the government.

For proper functioning, the government needs to be divided into various departments. Each department is specialized to handle their own issue, e.g., the department of housing deals with housing issues ensuring most citizens with decent and fair housing (at least that is what they are supposed to do). The department of finance on the other hand, is supposed to solve financial problems of the state. These two departments should talk to each other every so often to figure out optimal solutions. If the ideal house costs the government a fortune, then the department of housing is definitely not consulting the department of finance about the costs. On the other hand if the state debt becomes so high that most people cannot afford decent houses, then we can be sure that the department of finance is not talking enough with the department of housing to ensure affordable houses.

As one can imagine, our brain can also be categorized as a small-world network. This is because it is known to be extremely efficient in compartmentalizing and integrating information. The extent to which a network is small-world can be measured by **small-worldness** which compares clustering-coefficient and path-length of the graph to that of a random graph. [Nakamura et al., 2009], used this concept successfully to exhibit that 'small-worldness' increases in the recovery process of patients suffering from Traumatic Brain Injury (TBI). Another way of measuring small-worldness of a network is to calculate **global efficiency** which signifies the network's ability to transmit information. This parameter has been used to show the effect of ageing in frontal and temporal regions of the brain.

Most of the parameters described above can only be applied on unweighetd networks losing a lot of information in the process. Also, most of the graph metrics deals with global differences, which might not be the case for a large number of cases. In fact, after performing a task, our brain should only show changes at a local level, since inducing global changes in the brain to perform a simple task is energy consuming. The few local measures are often complex in terms of their calculation and interpretation. Finally, we cannot use each and every voxel as a node for the graph since it will be computationally expensive. To overcome this challenge researchers often define groups of voxels or only care about particular regions and construct graphs from them. This assumption leads to a priori biases in the studies.

1.2.2.2 Seed-Based Approach

This approach is the most predominantly used 'local' method. It investigates the FC between the regions that have been chosen *a priori*, called **seed-region** or **region of interest (ROI)**. Another common approach is to investigate all the FC of the seed region or a group of ROIs. [Biswal et al., 1995] used this approach to discover resting-state. This technique relies on the extraction of time-series from the ROI and then characterizing the relationship with time-series of other voxels or other ROIs. The most basic step calculates the average value at each time point, arguably cancelling out the noise. More advanced method like Principle Component Analysis can also be used for this purpose. The next step is to define the relationship of the extracted time-series with those of others. Since I have talked about this in the previous section, I will not go into much detail here. When comparing two population or conditions using this method, the final step often involves performing t-test on the FCs and correcting for multiple comparisons. As one can see, this method gives more power by reducing the number of multiple comparisons.

This method has been incredibly helpful in recognizing functional subdivisions in striatum [Di Martino et al., 2008], ACC [Margulies et al., 2007], cerebellum [O'Reilly et al., 2010], amygdala [Roy et al., 2009] among other brain regions [Eckert et al., 2008, Margulies et al., 2007]. This feat has been possible with rsFC, since usage of task FC would have required meta-analyses to perform the same functional distinctions. This method has also been extremely beneficial in cross-species animal research. The DMN as well as parahippocampal network has already been identified in anesthetized monkey [Vincent et al., 2010] highlighting the evolutionary tracing of these networks. This technique has also been used to identify potential biomarkers in various neurological disorders (see above).

As we observed above, there is a predominance of DMN in the results. This highlights one of the major limitations of this method, which is the *a priori* selection bias. Even though, the ROIs used in the study are usually based on well-founded hypotheses, exploring new FCs with this method is quite difficult to achieve. This bias is compounded by the low sample size which is quite prevalent in the field of neuroimaging. Furthermore, the size and even shape of the ROI can lead to quite different results making the results of the same regions, inconsistent. This concern has been voiced by multiple reviews examining potential biomarkers of disorders [Hull et al., 2017, Greicius et al., 2007].

1.2.2.3 Independent Component Analysis Clustering

Independent Component Analysis (ICA) performs on the assumption that the brain can be organized into a number of discreet networks. These networks can be decomposed using blind source separation. Unlike seed-based approach, it provides the advantage of having minimal *a priori* selection. Another major advantage of ICA is that it requires minimal preprocessing since noise can be decomposed into a separate component. ICA can be applied on both spatial and temporal axes, however spatial ICA is most common since fMRI data consists of more spatial points than temporal ones. Performing ICA at a group level is quite challenging since same components have to be selected across all individuals. Multiple approaches are proposed to overcome this issue.

A very commonly used approach is **template matching**, where individual-level components are first discarded on the basis of temporal properties and then the rest are compared to a researcher-defined template for 'goodness-of-fit'. This step requires judgment of the researcher to define the template since gold-standards do not exist. A proposed solution to this issue is to perform group-level ICA on co-registered and concatenated individual datasets. This approach has been successfully used to characterize distinct cortico-cerebellar networks [Habas et al., 2009]. Another approach is **dual-regression ICA**, where after the creation of template, spatial regression is performed on the individual level to extract a temporal model for a second temporal regression. This method has been successfully used to identify distinct networks in resting-state brain [Zuo et al., 2010]. ICA has also been successfully used to identify biomarkers in Alzheimer's disease [Sorg et al., 2007], mild cognitive impairment [Qi et al., 2010], depression [Greicius et al., 2007], schizophrenia [Jafri et al., 2008], Huntington's disease [Wolf et al., 2008], lateral sclerosis [Mohammadi et al., 2009] temporal lobe epilepsy [Zhang et al., 2009b], and non-communicative brain damaged patients [Vanhaudenhuyse et al., 2010].

Although ICA is quite successful as a data-driven approach, its performance relies on possible interpretation of the components. This step asks the researchers to discard one of the components as 'noise component' adding *a posteriori* bias to the analysis. Another disadvantage of ICA is the complexity involved in calculating, especially for group-level ICA. Furthermore, the difficulty in interpretation of the components makes it quite challenging to obtain results with this method. Since ICA algorithm begins with a random assumption with each iteration, replication using ICA can be quite daunting. If we go back to the primary assumption of ICA that our brain consists of independent networks, we can see that the results obtained will suffer from a particular bias. Since our brain is known to have modules which are interconnected, such an assumption can be quite harmful. This concern has been voiced by [Daubechies et al., 2009] who argued that ICA is designed to detect sparsity of the brain modules instead of independence.

To eliminate the *a posteriori* selection bias induced by ICA, **clustering** method is gaining popularity in the field of neuroscience. Clustering refers to a set of mathematical tools which are designed to detect patterns in the data. Unlike ICA, which is designed to identify large-scale networks in the FC, clustering is designed to 'break' the brain network into smallest detectable distinct functional units. Mathematically, clustering refers to a family of techniques, which I would not elaborate in much detail. But any discussion on clustering is incomplete without its most prominent three approaches: hierarchical clustering, partitional clustering and spectral clustering. **Hierarchical Clustering** start by treating each data point as one cluster, and as the number of clusters is decreased these are merged together depending on their similarity. **Partitional Clustering** on the other hand works to identify all the clusters together at once. **Spectral Clustering** requires the performance of eigen-decomposition first as a data-reduction step and then uses standard partitioning procedures (like k-mean clustering) to obtain clusters.

[Cordes et al., 2002] has successfully used clustering methods to detect functionally distinct clusters of sensorimotor cortex, auditory cortex, fusiform gyrus and primary visual cortex, as well as 'nuisance' cluster signifying Cerebrospinal Fluid (CSF) and other nuisance covariates. Salvador and colleagues [Salvador et al., 2005], identified even more networks using anatomical location as a grouping criterion. Van den Heuvel et al. [van den Heuvel et al., 2008], recently used a more advanced clustering method in a group of 26 healthy participants to characterize seven distinct networks in rsFC. They also calculated a consistency matrix which quantified the frequency with which voxels were assigned to the same cluster across participants. Almost all of the studies using clustering algorithms are often limited because of the computational cost of the method. To overcome this issue, often studies reduced the volume of the data either by acquiring data from only a limited number of slices, rather than the whole brain (Cordes et al., 2002) or by resampling the brain according to a parcellation scheme (e.g., Salvador et al., 2005).

Another limitation of clustering techniques and ICA is the requirement of defining the number of components beforehand. This can be quite difficult since lower number of components will result into concatenation of two distinct networks together, or worse, breaking of a single component into two to accommodate them in already existing clusters. However, choosing a high number is computationally costly especially for group data. Just like ICA, the clusters can be often difficult to interpret and henceforth induces human judgment, making it subjective. We can see here that even though both ICA and clustering techniques offer respite from *a priori* selection bias, they both require *a posteriori* selection bias. This could be more beneficial in certain cases, but due to the complexity of these methods, the gain after using these methods has to be evaluated by the researcher themselves.

1.2.2.4 Multivariate Pattern Analysis

Multivariate Pattern Analysis (MVPA) has gained traction in the recent neuroimaging literature [Norman et al., 2006]. Like ICA and clustering techniques, MVPA looks for multi-voxel patterns. Information contained in these patterns can then be decoded by applying powerful pattern-classification algorithms. A major advantage of using MVPA arises from the fact that it is highly data-driven, not requiring any template to validate the data. This is often accomplished by dividing the data into two subsets, ’training set’ and ’testing set’. This requires the method to be used only for large data-set, which is difficult to obtain in neuroimaging studies. Using this method on typical neuroimaging samples of 20-30 subjects can lead to misleading results. Another problem of using this method is feature selection. This can be done mathematically [Singh et al., 2011]. However the features are then difficult to interpret and are computationally costly. On the other hand, manual feature selection (like limiting it to specific ROIs) will again lead to selection biases.

MVPA has been primarily used for disease-state prediction to successfully distinguish between healthy individuals and patients. Some well-known examples are its use in classifying ADHD [Zhu et al., 2008], Schizophrenia [Jafri et al., 2008] and Alzheimer's disease [Wang et al., 2006]. Due to its computational complexity this method remains to be less used and hence the limitations are still largely unknown. One specific question arises in mind regarding feature selection. While some studies using MVPA do compare features, they are used in a very narrow context, making it difficult to assess the strength and weaknesses of feature comparisons and the ideal methods to choose them. Another limitation comes from spatial resolution. While spatial resolution remains an important issue for most methods, it is of particular interest in case of MVPA. This is due to the fact that it looks for subtle patterns in the data. However, high spatial resolution makes it more difficult to calculate because of computational complexity. Another limitation is the difficulty of interpretation of the results.

1.2.2.5 "Local" Methods

Since we are talking about capturing 'local' effects, this section will remain incomplete without talking about amplitude of **low frequency fluctuations (ALFF)** and **regional homogeneity (ReHo)**. These two methods have gained quite some popularity in the neuroscience community. ALFF is defined as the total power in the low frequency range. Fractional ALFF (fALFF) is a measure depicting the ratio of the low-frequency power to the sum across the whole frequency range [Zou et al., 2008]. [Fan et al., 2013], used fALFF to show that depressed patients with suicidal tendencies had an increased fALFF in right STG and low fALFF in right ventral MFG. This made them claim right STG as a potential biomarker for suicidal tendencies in depressed individuals. This claim has been supported by Cao and colleagues [Cao et al., 2016], who also showed abnormal fALFF value for right STG in depressed patients with suicidal history.

ReHo was originally proposed by Zang and colleagues [Zang et al., 2004] to measure coherence/homogeniety of a given voxel with its nearest neighbours. Homogeneity is measured using Kendall's coefficient of concordance, a similarity measure which uses ranking. Pattern of networks in rsFC obtained by ReHo has been shown to be similar to DMN [Long et al., 2008]. This method has been successfully used to show decreased Reho values in bilateral frontal, temporal, occipital, cerebellar posterior, right parietal and left limbic lobes in patients suffering from Schizophrenia [Liu et al., 2006]. It has also been successfully used to characterize boys suffering from ADHD [Cao et al., 2006]. Both Reho and fALFF methods are quite useful however they come with their own set of caveats.

ALFF measurements have been shown to be higher in grey matter than white matter [Biswal et al., 1995] inducing potential confounds. Other studies have shown that it can be affected by possible artefactual findings in the vicinity of blood vessels and cerebral ventricles [Zuo et al., 2010]. ReHo analysis on the other hand is affected by magnitude of spatial smoothing and the size of the ”neighborhood” [Zang et al., 2004].

In this section, I have reviewed the most widely used methods for analyzing rsFC. The one common feature in all the methods is that they come with their own pros and cons. There is a common pattern that clearly emerges though, and that is the need of a simple method which does not need any pre or post selection criterion. Banishing selection bias should not come at a cost of computational complexity. It is of no doubt that these methods whether they require some assumption or not, gives unique information about the human brain. They have been successful in wide-array of situations and have been tested and re-tested. However, the need for a much simpler method with higher sensitivity and without any bias is much needed. Higher sensitivity will increase the chances of detecting differences in rsFC, which in turn will allow us to be free from pre- or post-selection biases.

1.3 Scope of the Current Thesis

The current thesis introduces a new method aimed to be more sensitive than traditional methods. The method called Link-Wise Analysis (LWA) is tested in the second chapter using simulations, where it is compared with traditional t-tests to detect differences in the rsFC. The limitations of both these methods are explored with respect to number of subjects, brain parcellation, and deviation of the FC distribution from normal distribution. By simulating various conditions, we showed that LWA has the potential to detect resting-state functional brain links that are significantly different. This chapter finishes with an application on a previously published data-set [Hlinka et al., 2011, Mantini et al., 2012, Ponce-Alvarez et al., 2015, Gilson et al., 2017]. The goal of the application was to find rsFCs that are significantly different in resting state vs natural viewing of a movie. The next two chapters are applications of this method with different designs.

The goal of using three different designs is to show the versatility of LWA. Traditionally, neuroimaging methods are only tested in classical two group designs. However, the current thesis goes further by demonstrating the power of a simple method like LWA to detect rsFC in more complex designs. To this end, the third chapter presents a study design with two groups and two resting-state scans increasing the complexity and thereby decreasing the power of analyses methods.

The fourth chapter shows another design altogether, where significant correlations between rsFCs and social-hierarchy perception are explored. Adapting LWA to detect significant correlations instead of differences takes it a step further.

To further elaborate, the goal of the third chapter is to find FC(s) which is responsible for statistical learning. For this purpose 36 right-handed participants listened to a four-minute audio either depicting artificial language or random audio stream. Resting-state scans were obtained before and after the stimuli. After performing LWA, we obtained a significant FC between left SPL and right PCC, revealing a link which might have been undetected with seed-based or cluster-based approaches. The fourth chapter is aimed to find FC(s) which is significant for social hierarchy perception. For this project, we combined event-related potentials (ERPs) and rs-fMRI obtained for 20 individuals. Participants played a game with simulated player who was either superior or inferior (previously used in [Santamaría-García et al., 2015]. Social-hierarchy perception was measured using ERPs [Santamaría-García et al., 2013] which was in-turn investigated for correlation with all the possible rsFCs. Using LWA, we showed the significance of the link between right Insula and left Parahippocampal Gyrus as well as, left MFG and left Superior Temporal Sulcus (STS) for social hierarchy perception.

Along with the versatility of LWA, the results from the three applications provide a very interesting picture of the resting-state brain. Both these issues are discussed in the Discussion which ties all the results together to formulate a clearer picture of the rsFC. Finally, this thesis hopes to add a new simple and effective method in the neuroimaging literature. Even though the applications here are only on rsFC, LWA can also be used for other modalities and combined with other methods.

Chapter 2

IDENTIFYING SALIENT FUNCTIONAL BRAIN LINKS BY MEANS OF MEDIAN SPLIT

Pallabi Sengupta, Gorka Zamora-López, Miguel Burgaleta,
Maurizio Corbetta, Gustavo Deco, Nuria Sebastian-Galles

2.1 Introduction

Different regions of our brain communicate with each other to perform various functions signifying the underlying functional 'connectivity' required to perform the cognitive tasks. Understanding this brain connectivity between different brain regions is investigated as the temporal dependency of the two brain regions and has become quite important in the field of neuroscience. This can be observed by numerous findings of differences in the functional connectivity of healthy individuals when compared with several neuropsychiatric disorders like Alzheimer's disease [Liu et al., 2008], Attention Deficit Hyperactivity Disorder [Konrad and Eickhoff, 2010], Autism Spectrum Disorder [Kennedy et al., 2006, Weng et al., 2010], Schizophrenia [Li et al., 2012] among others [Mulders et al., 2015, Dichter et al., 2014, Greicius, 2008]. Another application of comparing functional connectivity occurs in understanding the effectiveness of various drugs by comparing the functional connections at 'rest' before and after the drug administration [Cera et al., 2014]. Moreover, comparing functional connectivity of participants performing social tasks, in the presence of two different kind of social hierarchy is yet another application of functional brain connectivity aimed to understand cognitive processes like social hierarchy perception [Zink et al., 2008].

These examples highlight the importance of understanding functional connectivity in a *case-control* design, where one group of participants is compared to the other (e.g., patients vs healthy) or two conditions are compared (e.g., before vs after administration of drug). The information obtained by these comparisons could either be global information or local information. Information at a global level focuses on the topological properties of the neural network using graph theoretical tools [Li et al., 2012]. However, global scale differences could only be the result of large scale changes in the brain connectivity network requiring large amount of energy. Such changes would be absent in normal day to day cognitive processes [Ponce-Alvarez et al., 2015] limiting the scope of such studies. Local level information on the other hand, deals either with activation or deactivation of certain brain areas [Zink et al., 2008] or changes in functional connections [Li et al., 2014b].

A major hindrance in exploring these local changes in functional connectivity is the number of multiple comparisons required to capture the true effect. This is especially true in the case of investigating functional connections since increasing the number of functionally separate brain regions in a study via different parcellation usage will lead to an exponential rise in the number of functional connections giving rise to more number of corrections required. To elaborate further let us take an example of a study employing a parcellation of 50 brain regions. This will give rise to $\binom{50}{2} = 1225$ functional connections. If we wish to increase the spatial resolution of the study by using a brain parcellation of 100 regions, the number of functional connections would be $\binom{100}{2} = 4950$. If the study focuses on exploring activation or deactivation at a higher spatial resolution then the number of corrections required would only double in number, while in case of functional connections it would be quadruple.

Different methods are used by researchers that tries to solve this problem of multiple comparisons. One of the most common methods is to preselect the functional connections on the basis of existing literature in the topic. This leads to *a priori* bias in the results, which is solved by clustering methods like Independent Component Analysis or other clustering techniques. However, after the analysis researchers would often have to interpret the clusters giving rise to *a posteriori* bias. Another set of methods focuses on pattern analyses, which are the most data-driven methods, but are often complex to use and require large amount of time. This mandates a new method which does not demand pre or post selection biases without increasing the complexity of the analysis. The current study addresses this issue by proposing a new method to explore salient functional connections in a case-control scenario.

The new method uses median-splitting to threshold the correlation values of the functional connections aimed to increase sensitivity of the statistical analysis. Median splitting has been successfully used previously to determine the effect of gesture sequences in captive chimpanzees [McCarthy et al., 2013], glycoprotein inhibitors and heparin for myocardial infarction [Kastrati et al., 2011], driving behavior in teenagers using a Bayesian Model [Kim et al., 2013] among others [MacCallum et al., 2002]. The contribution of this paper hence is validating median-splitting to identify salient functional brain links in a case-control scenario by comparing its performance to traditional methods used on weighted functional connections like Student's t test or Mann-Whitney U test. For the sake of simplicity we call this method Link Wise Median Splitting and we call the traditional Student's t or Mann Whiteny U test as Link Wise Weighted Test.

The paper is mainly divided into two sections: in the first section we tested the performance of Link Wise Median Splitting and compared it with Link Wise Weighted Test by simulating differences in functional brain links; in the second section we applied Link Wise Median Splitting in a real case-control scenario comparing resting state connectivity with functional imaging acquired while subjects were watching a movie mimicking natural viewing. The case-control data has been used previously to test Gaussanity of functional connectivity values [Hlinka et al., 2011], compare natural-viewing activity correlation between human and monkey subjects [Mantini et al., 2012], explore spontaneous synchronization networks [Ponce-Alvarez et al., 2015] and, investigate cortical Effective Connectivity [Gilson et al., 2017]. By the aid of simulations, we showed that the Link Wise Median Splitting is much more sensitive to true differences and therefore, increases the chances of identifying significant changes in functional connections. This finding is bolstered by the results obtained in the case-control application data-set, where Link Wise Median Splitting successfully identified salient links, while the non-parametric method failed to do so. It is important to remember that Link Wise Median Splitting can be used to explore salient connections in any imaging modality since it does not use any assumptions pertaining to the calculation of the brain connections.

2.2 Methods

The goal of this paper is to detect salient links without any selection bias before or after the analysis. To achieve this we propose a new method called Link Wise Median Splitting (LW-MS) and compare it with traditional methods used on with the correlation values of the functional connections, which we call Link Wise LW-WT (LW-WT). To perform LW-MS and LW-WT the functional connectivity (FC) matrices are needed to be computed first using Pearson's correlation between all possible node combinations giving rise to an $N \times N$ matrix, where N is the number of brain regions. The i^{th} and the j^{th} component of the matrix denotes the temporal dependence between the i^{th} and the j^{th} brain regions. These FC matrices are then transformed using Fisher's r to z transformation which ensures normality [Fisher, 1995, Valencia et al., 2009]. There can also be other ways of calculating FC matrices using mutual information [Bassett et al., 2009], transfer entropy [Vicente et al., 2011], phase synchronization [Kitzbichler et al., 2009, Palva et al., 2010], or synchronization likelihood [Stam, 2004], which can give information about non-linear trends unlike Pearson's correlation.

2.2.1 Analysis Methods

Since the methods would be the same across all links, here we focused on the performance of the two methods on only one link, which is different across two populations A and B. To perform LW-MS, the first step was to threshold the FC matrices. Threholding was done at link level by using median splitting where every link was thresholded using the median value of that specific link after concatenating the group of subjects together. All the link values higher than the median were then denoted as 1 and those who were below the median were denoted as 0. This lead to the number of subjects in population A with link value 0 to be A_0 and the number of subjects in population A with link value 1 to be A_0. For population B, the number of subjects with the link value denoted as 1 and 0 were B_1 and B_0, respectively. This data was used to construct contingency table (Table 2.1). The p value obtained by using Fisher's Exact Test was then corrected for multiple comparisons encompassing all possible links using Bonferroni's correction. In case of LW-WT, we performed Mann Whitney U Test to ensure that non-normality (if any) of the data sets would not affect the outcome. Similar to LW-MS, the p value obtained after performing the Mann Whitney U test was corrected for multiple comparisons using Bonferroni's correction.

	No. of subjects with link value 0	**No. of subjects with link value 1**
Population A	A_0	A_1
Population B	B_0	B_1

Table 2.1: Contingency table used by LW-MS to determine the significance of each link between two populations A and B.

2.2.2 Performance Evaluation

To compare the performance of LW-MS with LW-WT in a case-control scenario, we created two different distributions X and Y mimicking a functional brain link from two different groups. The aim was to investigate the performance of LW-MS and compare it with that of the LW-WT. We varied the mean (μ) and the skewness (γ) of the distributions for this purpose. We also varied the number of data points in each distribution from m = 10 to m = 150, mimicking the number of subjects. We iterated each and every scenario 10,000 times to have a proper estimation of the sensitivity of the two methods. For all the scenarios, we assumed the number of nodes to be, N = 100, until explicitly stated otherwise, leading to $\binom{100}{2} = 4950$ unique functional brain links. Hence, we corrected for 4950 multiple comparisons using Bonferroni's correction and calculated the number of times the corrected p value obtained by each method was $p \leq 0.05$. The detection rate, in percentage, was then obtained by normalizing the number of time corrected p was significant by 10,000.

Case 1: To test the detection rate as a function of the difference of means, $\mu(X)$ and $\mu(Y)$, we varied $\mu(X)$ from -1 to 1 while keeping $\mu(Y)$ constant at 0 (Figure 2.1(a)). We kept the other parameters like skewness (γ), kurtosis (κ) and, variance (σ) constant (γ = 0, κ = 3, σ = 1).

Case 2: Since real data can sometimes be skewed, the distributions X and Y were created with different skewness values while keeping the remaining parameters constant ($\mu(X)$ = 0, $\mu(Y)$ = 1, κ = 3, σ = 1). The skeweness of Y was kept to $\gamma(Y)$ = 0, similar to normal distribution, while $\gamma(X)$ was varied from -1 to 1 (Figure 2.1(b).

Case 3: Since a higher number of nodes should lead to a larger number of unique links and therefore, larger number of multiple comparisons, we also examined the effect of altering the number of nodes, N. We chose two effect sizes -1 and 0.5, to check whether the effect size also modulates the relationship of sensitivity with N. We varied the number of nodes from N = 50 to N = 1000 while keeping the rest of the parameters constant ($\mu(X)$ = 0, $\mu(Y)$ = 1/-0.5, κ = 3, σ = 1).

Case 4: Finally, we explored the effect of altering the number of subjects on the sensitivity of the two methods further by considering a range of m = 5 to m = 11 data points per link, mimicking the presence of only 5 to 11 subjects in each group. Even though such small data-sets are undesirable in studies, this extreme

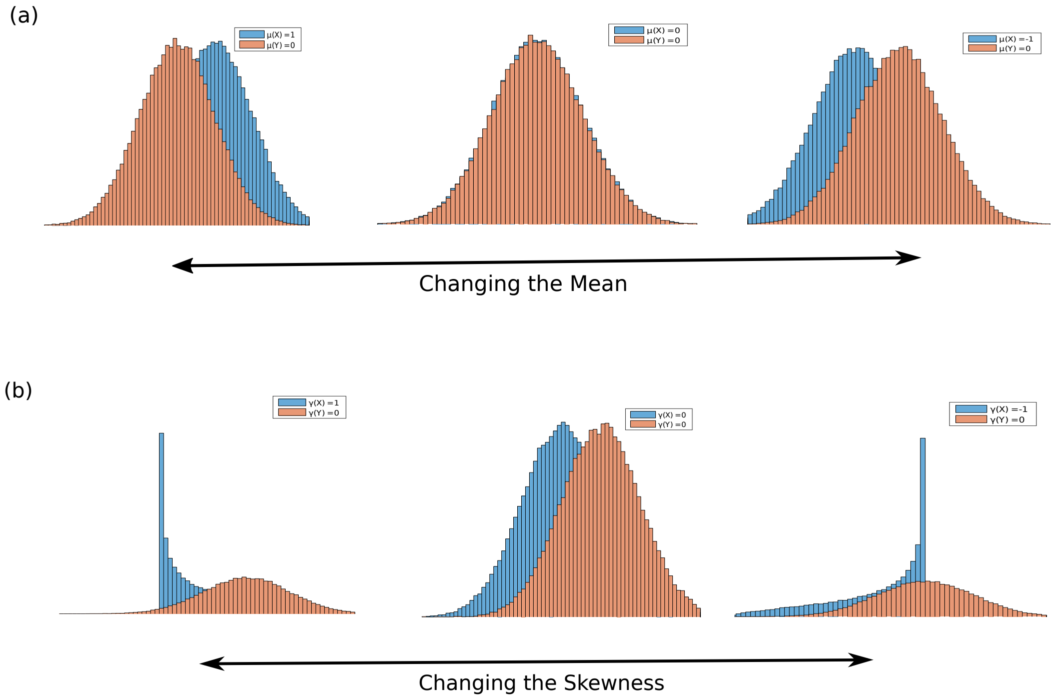


Figure 2.1: We wanted to test the detection rate of the two methods, LW-MS and the LW-WT while changing the parameters of the distributions: (a) Mean of distribution X is changed from $\mu(X)$ = -1 to $\mu(X)$ = 1; (b) Skewness of distribution X is changed from $\gamma(X)$ = -1 to $\gamma(X)$ = 1

case explored the possible limitations of LW-MS and the LW-WT. We contrasted the results with sample sizes of m = 10 to m = 150.

2.2.3 Control Case-Study

In order to provide a real test-case and to compare the performance of LW-MS with that of the LW-WT, we applied the two methods to a previously published dataset. The experimental setup consisted of measuring functional magnetic resonance during rest and during viewing of a movie for a cohort of participants. Using this data-set Gaussanity was observed in FC measures [Hlinka et al., 2011]. The same dataset has also been used to show the similarities between natural-viewing neural correlates of humans and monkey (by [Mantini et al., 2012]), to show the temporal alternation of spontaneous synchronization communities in resting state FC [Ponce-Alvarez et al., 2015] and to show an increment in homotopic connections in temporal and parietal areas during natural viewing [Gilson et al., 2017].

2.2.3.1 Participants

24 right-handed young, healthy participants (15 females, 20-31 years old) took part in the study. They were informed about the experimental procedures, and signed a written informed consent. The procedures were approved by the Ethics Committee of the Chieti University. We obtained resting state scans with eyes opened and a natural viewing condition for 22 participants. 2 participants were discarded because they only had recordings at rest. In the resting state, participants were instructed to fixate on a red target with a diameter of 0.3 visual degrees on a black screen. Participants watched 30 minutes of the movie 'The Good, the Bad and the Ugly' in a window of 24 × 10.2 visual degrees for the natural viewing condition. Participants viewed the movie through a mirror tilted by $45°$while it was projected on a translucent screen using an LCD projector. Auditory stimuli were provided using MR-compatible headphones.

2.2.3.2 Data acquisition

A 3T MR scanner (Achieva; Philips Medical Systems, Best, The Netherlands) at the Institute for Advanced Biomedical Technologies in Chieti, Italy was used to obtain functional images. T2*-weighted echo-planar images (EPI) with BOLD contrast using SENSE imaging was used to obtain functional images. 32 axial slices were acquired in ascending order, covering the entire brain (230 × 230 in-plane matrix, TR/TE=2 s/3.5 s, flip-angle = $90°$, voxel size=2.875 × 2.875 × 3.5 mm3). For each subject, 2 scanning runs of 10 minutes were obtained for resting state while for natural viewing 3 scanning runs of 10 minutes were obtained. However, for the purpose of the current study only the first 2 movie scans were used for a fair comparison between the rest and the natural viewing condition. Each run had 5 dummy volumes - allowing the MRI signal to reach steady state and an additional 300 functional volumes that were used for analysis. During scanning, eye position was monitored using a pupil-corneal reaction system at 120 Hz (Iscan, Burlington, MA, USA).

2.2.3.3 Preprocessing

Data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB (The Mathworks, Natick, MA). The preprocessing steps involved: (1) slice-time correction (2) correction of head-motion, (3) coregistration of the 90 mean functional image, and (4) spatial normalization of all images to a standard stereotaxic space (Montreal Neurological Institute, MNI) with a voxel size of $3 \times 3 \times 3mm^3$. Artifacts related to blood pulsation, head movement and instrumental spikes were removed by using spatial independent component analysis (ICA) on the BOLD time series. This procedure was performed by using the GIFT toolbox (Medical Image Analysis Lab, University of New Mexico). No global signal regression or spatial smoothing was applied. We extracted the mean BOLD time series from the N = 66 regions of interest (ROIs) of the brain 100 atlas used in [Hagmann et al., 2008], for every subjects per condition. These time series were used to calculate the Functional Connectivity (FC) matrix using Pearson's correlation coefficient. The FC matrices were transformed using Fisher's z transform to normalize correlation values.

2.2.3.4 Statistical Analysis

To explore the possible functional brain links that are significantly different between resting state and natural viewing, we extracted 2145 unique links from the FC matrices. Each of these links were thresholded using their own median so that link values higher than the median were considered to be 1 and those which were lower were considered to be 0. On each of these thresholded links, we performed Fisher's Exact test to investigate the relationship between condition (rest vs natural viewing) and binarized link value. To compare our results we also performed Mann-Whitney U test on the unthresholded values of each link. For both analyses, we corrected for multiple comparisons using Bonferroni's correction and looked for significant links at $p \leq 0.05$.

2.3 Results

The goal of the present paper is to detect salient links that are significantly different in a case-control scenario. To do this we tested the performance of two methods Link Wise Analysis (LW-MS) and Weighted Method. We started by testing the performance and limitations of the method by numerically simulating different scenarios in which either the properties of the distributions or the number of subjects or number of ROIs in the parcellation were altered. Then we showed the use of the method by applying it to a control dataset which has been previously well studied. It consists of the comparison between functional connectivity during rest and during natural movie viewing [Hlinka et al., 2011].

2.3.1 Performance Evaluation

In order to evaluate the limits of LW-MS with respect to variations in the properties of the link distribution, number of nodes and, number of participants, we simulated two distributions, X and Y. For each variation of these parameters, we calculated the detection rate of significantly different functional links. We looked into roughly four case situations pertaining to alterations in terms of difference in mean (μ), skewness (γ), number of nodes (N) and, number of subjects (m).

As mentioned in the Methods Section, the first case scenario investigated was the effect of mean (μ) and number of subjects (m). For this purpose, we varied mean of one of the distributions from $\mu(X)$ = -1 to $\mu(X)$ = 1, while keeping the other one constant at $\mu(Y)$ = 0. We also varied the number of subjects m = 10 to m = 150 to see whether the sensitivity of the method can be modulated by the number of subjects. We calculated the detection rate for each scenario and exhibited the results in heatmap (Figure 2.2(a) and Figure 2.2(b)). Different colours represent different detection rates in the heatmap, where the green end represents lower detection rate while the yellow end represents high detection rate. We observed from the heatmaps in Figure 2.2(a) and Figure 2.2(b), that performing LW-MS was beneficial to determine salient links that are significantly different in FC. We observed that the detection rate remained high even for lower number of subjects (m = 25) in case of LW-MS while for LW-WT the detection rate dropped pretty quickly irrespective of the difference in mean. The picture became clearer for snapshots at different values of $\mu(X)$. For both extremities, i.e., when $\mu(X)$ is either 1 or -1 (Figure 2.2(c) and Figure 2.2(d)), LW-MS performed better than LW-WT especially for low sample sizes. LW-WT became almost as sensitive as LW-MS when the number of subjects for each group reached m ≈ 60. The difference between the two methods became clearer for lower mean values of $\mu(X)$ = 0.5 and $\mu(X)$ = -0.5 (Figures 2.2(e) and Figure 2.2(f)), where LW-WT never became as sensitive as LW-MS. However, the detection rate was also lower for these scenarios.

Since most real distributions do not satisfy the assumption of normality very strictly, we also looked into the effect of skewness (γ) in our second scenario. Similar to the first scenario, we varied the skewness of the distribution X from $\gamma(X)$ = -1 and $\gamma(X)$ = 1, while keeping $\gamma(Y)$ constant at 0. Like in the first case, we again varied the number of subjects from m = 10 to m = 150. We calculated the detection rate for each scenario and exhibited the results in heatmap (Figure 2.2(a) and Figure 2.2(b)) with same color code as Figure 2.2(a) and Figure 2.2(b). As observed in the heatmaps in Figure 2.3(a) and Figure 2.3(b), the difference in performance was not that different for the two methods across different skewness differences. However, detection rate of LW-MS was higher than LW-WT when the number of subjects ranged from m = 20 to m = 30. We also observed that the difference between the two methods were not modulated much by the value of difference in skewness (Figure 2.3(c), Figure 2.3(d), Figure 2.3(e) and, Figure 2.3(f)). We did observe however, that both methods were affected by the direc-

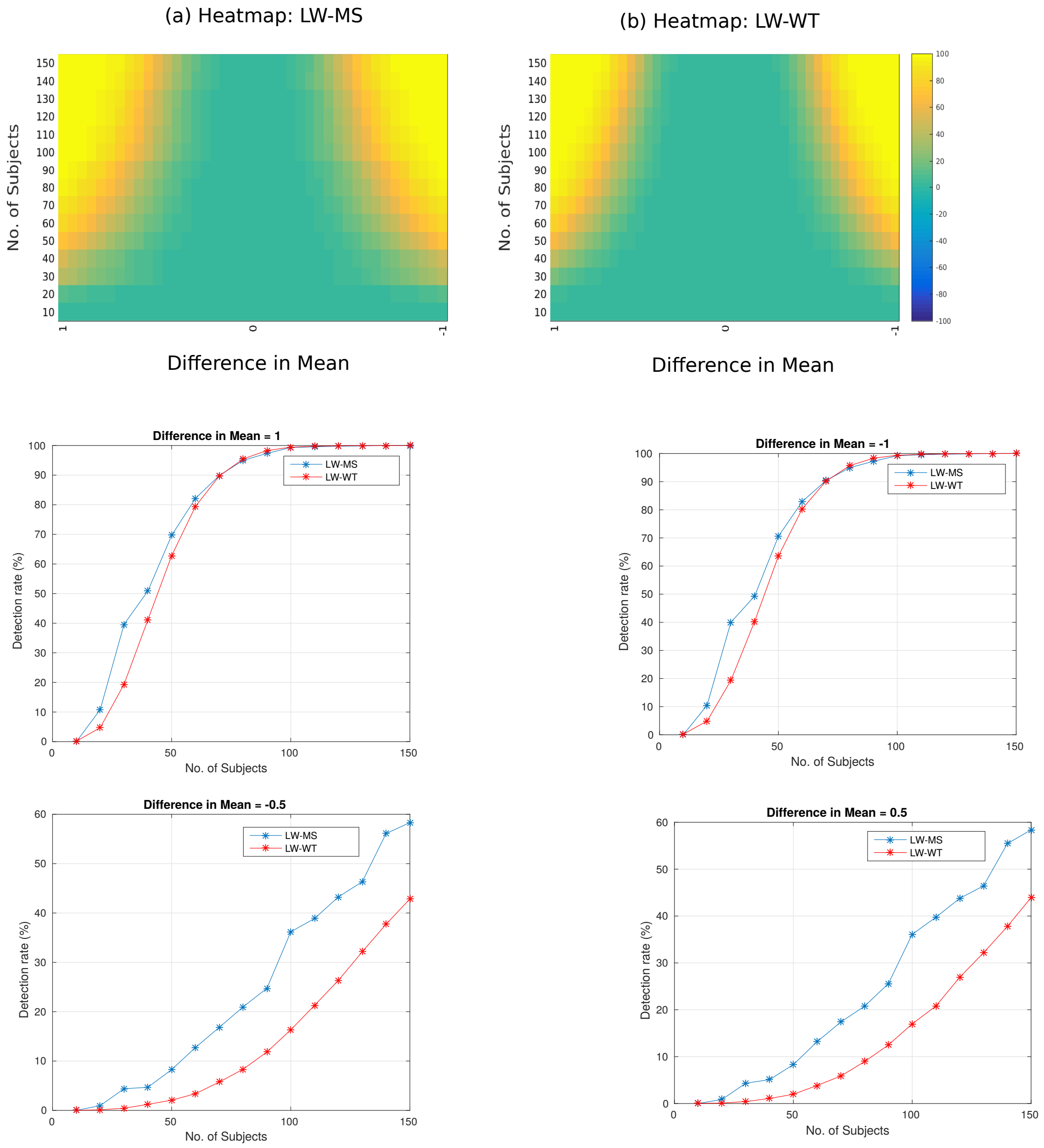


Figure 2.2: Detection rate changes with the difference in the mean (μ) and number of subjects (m) in the data. Heatmaps of the detection rate are shown for (a) LW-MS and (b) LW-WT. The colorbars represent the detection rate where the green end represents low number of detection of the true difference while the yellow end represents high detection rate. Slices of the heatmap showing difference in detection rate of the two methods are observed for four different scenarios: (c) Difference in mean = 1 ($\mu(X)$ = -1, $\mu(Y)$ = 0), (d) Difference in mean = -1 ($\mu(X)$ = 1, $\mu(Y)$ = 0), (e) Difference in mean = 0.5 ($\mu(X)$ = -0.5, $\mu(Y)$ = 0) and, (f) Difference in mean = -0.5 ($\mu(X)$ = 0.5, $\mu(Y)$ = 0). The differences are more pronounced for lower effect sizes; however the detection rate is also lower.

tionality of the skewness (Figure 2.3(e) and Figure 2.3(f)). We observed this only for smaller value of skewness ($\gamma(X)$ = 0.5 and $\gamma(X)$ = -0.5). Even though the sensitivity of the two methods became similar when the number of subjects in each group was m ≈ 90, a different trend emerged when the difference in skewness was -0.5. At this difference, LW-WT performed mildly better than the LW-MS when the number of subjects were in the range of m = 80 to m = 100. When the number of subjects was m = 100, the two methods performed similarly. This makes us suspect that the performance of LW-MS is modulated by the direction of skewnes, when the difference of skewness of two distributions is small.

We then studied the performance of the methods when the number of nodes (N) is varied resulting from different parcellation. Since higher number of nodes will lead to higher number of unique brain links and therefore, higher number of multiple comparisons, we were interested in exploring the limitations of the two methods in terms of number of nodes. We can clearly see from Figure 2.4(a) that the sensitivity of the LW-WT decreased gradually with increasing number of nodes. On the other hand, the sensitivity of LW-MS decreased in steps. Even though the detection rate of the true difference remained higher for LW-MS, one can extrapolate the trend and speculate that for extremely high number of nodes the two methods will be similar in terms of their detection rates. We observed a similar trend even for smaller difference in mean ($\mu(X)$ = 0.5, $\mu(Y)$ = 0). However for smaller difference in the mean, the detection rate was also lower (Figure 2.4(b)).

Finally, to determine the limitations of the LW-MS and LW-WT with respect to the number of subjects, we varied the number of subjects in the range of m = 5 to m = 11 along with m = 10 to m = 100 while keeping the other parameters constant. As evident in Figure 2.4(a) and Figure 2.4(b), differences in the detection rate are inversely proportional to the number of subjects. Also, we observed that when the number of subjects was relatively high, i.e, m $>$ 70, the detection rate of the two methods converged. Another observation was that both methods reached their lowest limit when m = 10. For very small samples, e.g., m = 5, the LW-WT became better at detecting salient links, see Figure 5b. However, the detection rate was of both methods was smaller than 1%, and thus negligible. We found a sudden jump in the detection rate of LW-MS when the sample size became m $>$ 10 while the power of LW-WT increased slowly. Now that we have shown that LW-MS is more sensitive than the LW-WT in different scenarios, in the next section we applied both methods to a dataset comparing resting state to natural viewing (Hlinkaa et al., 2011) to compare their applicability.

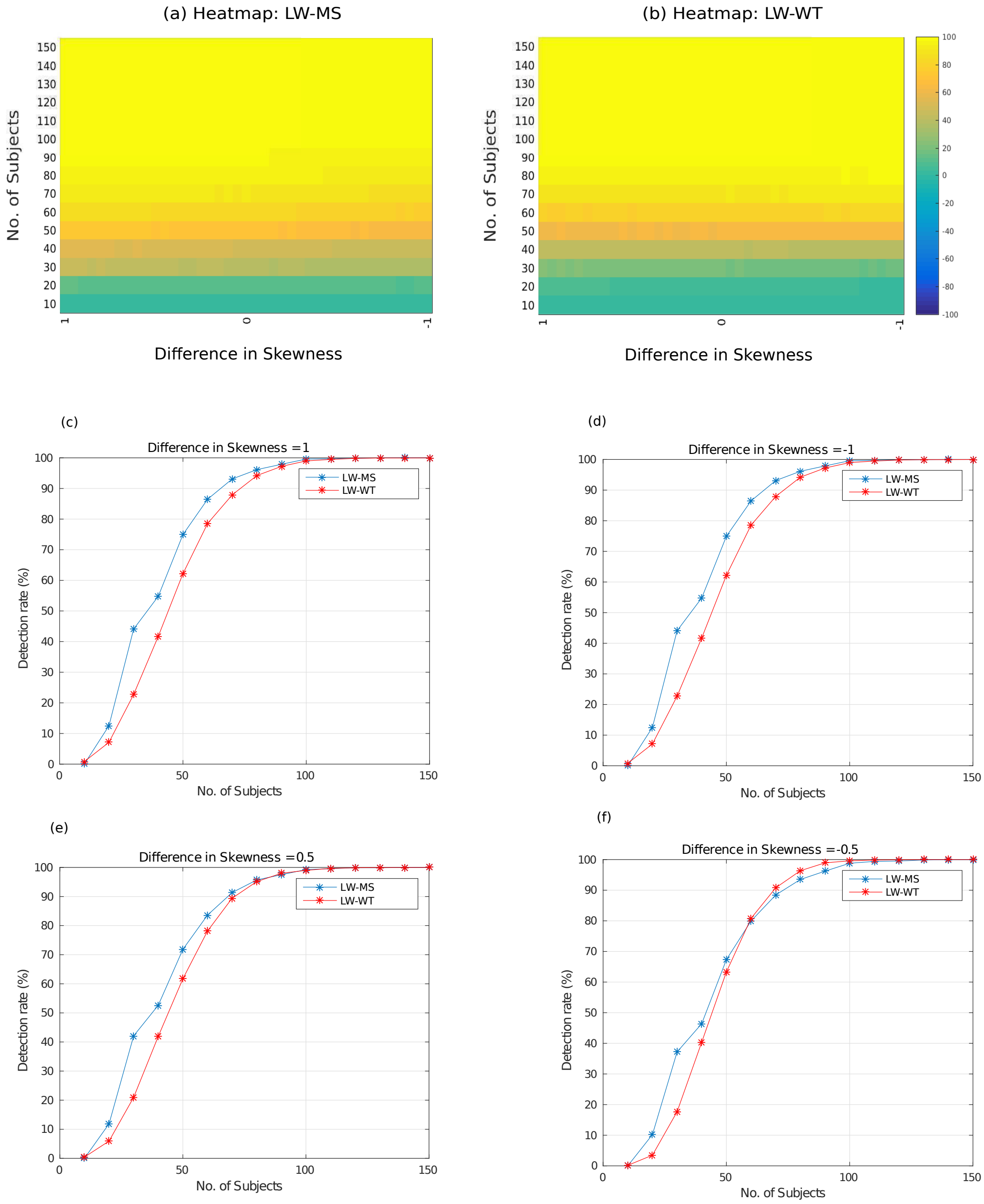
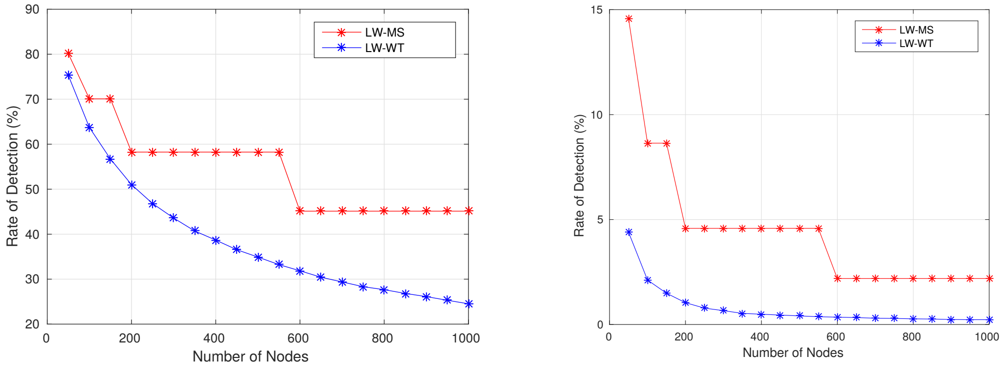


Figure 2.3: Effect of skewness (γ) on the percentage of detection of true difference varies with the number of subjects as shown by heatmaps for (a) LW-MS and (b) LW-WT. Again, the colorbars represent the detection rate where the green end represents low number of detection of the true difference while the yellow end represents high detection rate. Skewness of one of the distribution is kept constant at 0, while the other is changed. The slices of the heatmap showing difference in detection rate of the two methods are observed for four different scenarios: (c) Difference in skewness = 1 ($\gamma(X)$ = 1, $\gamma(Y)$ = 0), (d) Difference in skewness = -1 ($\gamma(X)$ = -1, $\gamma(Y)$ = 0), (e) Difference in skewness = 0.5 ($\gamma(X)$ = -0.5, $\gamma(Y)$ = 0) and, (f) Difference in skewness = -0.5 ($\gamma(X)$ = -0.5, $\gamma(Y)$ = 0).



(a) Effect Size = -1

(b) Effect Size = 0.5

Figure 2.4: Effect of the number of nodes on detection rate when (a) difference of mean is -1 ($\mu(Y)$ = 0, $\mu(X)$ = 1), (b) difference of mean is -0.5 ($\mu(Y)$ = 0, $\mu(X)$ = 0.5). As the number of nodes increases, so does the number of multiple comparisons leading to a decline in power. The decline is gradual for LW-WT whereas for LW-MS, it decreases in steps. The sensitivity of LW-MS however, aLW-MSys remains higher than the LW-WT.

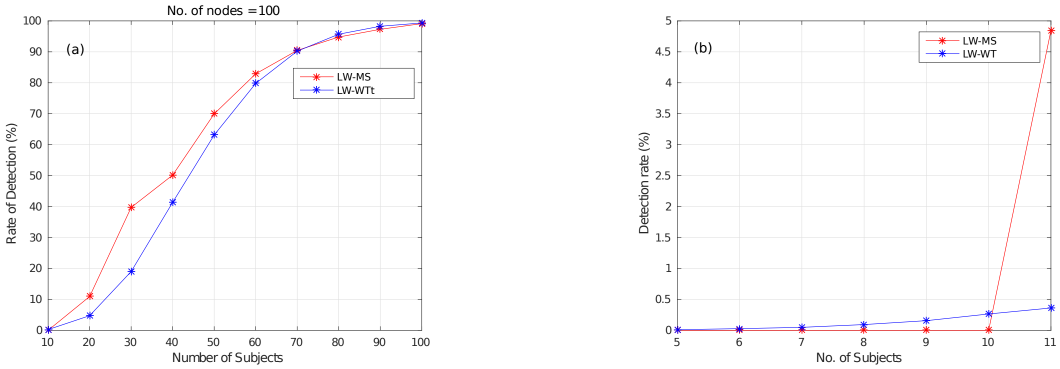


Figure 2.5: Variation of detection rate with the number of subjects (m): (a) m = 10 - 100; and (b) m = 5 - 11. We kept the number of nodes to be constant at 100. The difference between the two distributions were also kept constant in terms of skewness, variance, and kurtosis and the difference in the mean was 1.

Sl. No.	Link	Uncorrected p value
1	right Parahippocampus Gyrus (rPG) - left Pars Opercularis (lPO)	2.0484×10^{-8}
2	right Parahippocampus Gyrus (rPG) - left Supramarginal Gyrus (lSpG)	1.6751×10^{-6}
3	right Caudal Anterior Cingulate Cortex (rcACC) - left Superior Parietal Lobule (lSPL)	1.6751×10^{-6}
4	right Posterior Cingulate Cortex (rPCC) - left Superior Parietal Lobule (lSPL)	1.6751×10^{-6}

Table 2.2: The functional brain links that were significantly different in rest vs natural viewing conditions along with the uncorrected p value. All these links were identified using LW-MS while the LW-WT failed to identify any.

2.3.2 Practical Application Results

As outlined in the Methods section we compared resting state FC with FC obtained during natural-viewing using LW-MS and the LW-WT. The goal was to detect salient links that were significantly different without using a pre or post selection bias. After correcting for multiple comparisons, LW-MS identified four functional brain links (Figure 6) to be significantly different between resting state and natural viewing conditions: 1) right Parahippocampus Gyrus - left Pars Opercularis (uncorrected $p = 2.0484 \times 10^{-8}$), 2) right Parahippocampus Gyrus - left Supramarginal Gyrus (uncorrected $p = 1.6751 \times 10^{-6}$), 3) right Caudal Anterior Cingulate Cortex - left Superior Parietal Lobule (uncorrected $p = 1.6751 \times 10^{-6}$) and, 4) right Posterior Cingulate Cortex - left Superior Parietal Lobule (uncorrected $p = 1.6751 \times 10^{-6}$). Thus, there were two triads at play, one connected by right Parahippocampal Gyrus and the other by left Superior Parietal Lobule. No links were identified using LW-WT.

2.4 Discussion

The identification of significant differences at the population level in the functional connectivity is a very important issue. Observing these differences while comparing patients with healthy population, can help us identify potential biomarkers for various disorders. And for healthy population cohorts, FC differences between resting state before and after a task or even comparing resting state with a task, similar to the case-study used here, can reveal precious details about the neural mechanisms underlying different cognitive processes. Studies have looked

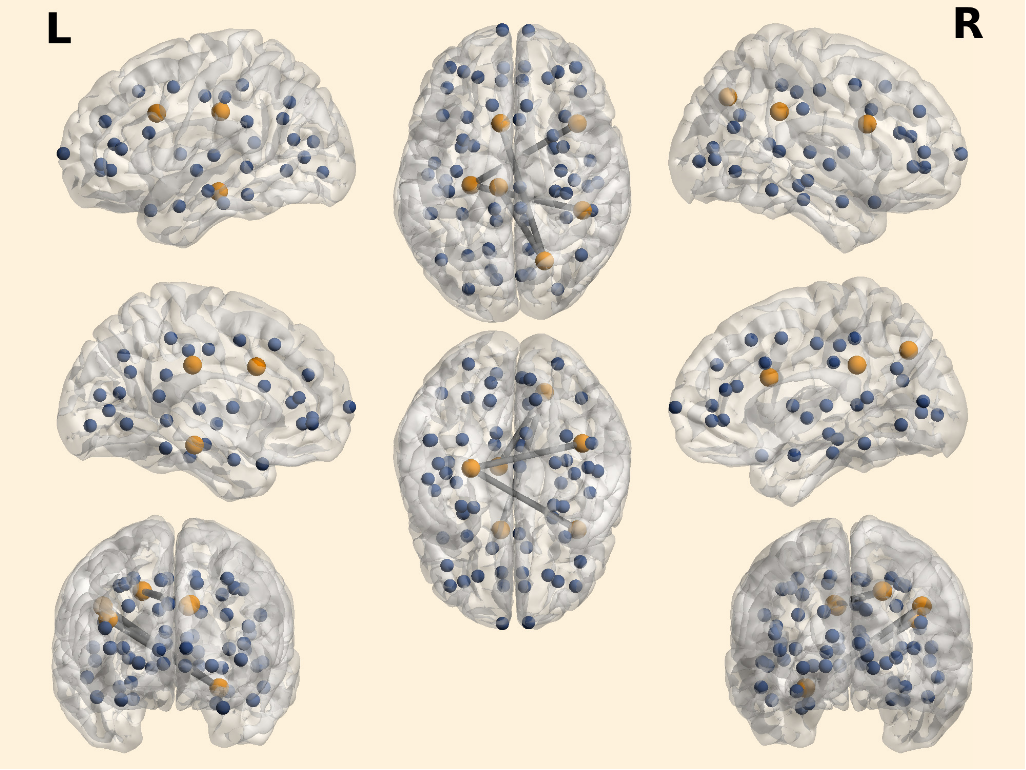


Figure 2.6: The links obtained by performing median splitting. No links were identified using Mann-Whitney U test on non-thresholded data after correcting for multiple comparisons. Two different triads are obtained one linked with right Parahippocampal Gyrus and the other with left Superior Parietal Lobule. We used BrainNet Viewer developed by [Xia et al., 2013] to show the functional brain links.

into these differences at a global level using graph theoretical applications while studies looking into local processes have often used pre or post selection biases to explore salient functional links. However, these approaches do not let us examine all the functional connections, potentially loosing precious information. In this study we tested the use of median splitting for every link which increases the sensitivity of capturing significant differences among all potential functional connections. In this way we can ensure that all brain links are investigated without loosing statistical power. We also applied LW-MS to successfully detect salient links between auditory, linguistic, visual and attention areas when resting state FC was compared with FC obtained during natural-viewing.

We noted that median splitting has been successfully used previously in other fields [McCarthy et al., 2013, Kastrati et al., 2011, MacCallum et al., 2002]. By simulating different scenarios, we showed that by using median splitting we increased the probability to detect true FC differences after correcting for multiple comparisons. It has been shown before that the use of a median split may enhance type I errors [Rucker et al., 2015, McClelland et al., 2015]; however we found that the detection rate of differences was 0% for both methods in the absence of a true difference. One can understand that this may be due to using Bonferroni's correction for multiple comparisons which is known to be particularly stringent. Another possibility is that the FC is not highly multicollinear, which has been shown to work well with median splits [Iacobucci et al., 2015]. But, this can be difficult to assume with linear correlations, which is used here.

The current study also highlighted some limitations of using both methods, the LW-MS and the LW-WT. Unsurprisingly, we observed that the number of subjects and the number of nodes affect the detection rate of both methods. We observed that for both LW-MS and LW-WT, sensitivity increased with high sample size. But LW-MS was able to detect salient links with high differences between the two distributions even when the sample size was m = 25 unlike LW-WT. For a sample size of m = 10 the detection rate of LW-MS dropped profoundly and the LW-WT is favoured. However, the overall detection rate of both methods was smaller than 1% at this point, and thus negligible. This strongly illustrates that studies with sample sizes smaller than 20 participants are unreliable. In respect with the performance sensitivity to number of nodes, the detection rate dropped gradually in case of LW-WT as expected. However, for LW-MS the detection rate lowered in steps regardless of the effect size. This is because the binarization employed by LW-MS is known to render step functions. Specifically, binarization typically gives rise to same p-value across a range of differences in mean of two distributions leading to a step function as observed here.

Another interesting observation was related to the modulations induced by changes in the skewness of the FC distributions. Unlike the mean effect size there were minimal variations over the change of skewness for both methods. Again we observed that unlike LW-WT, LW-MS performed better with low sample size of m = 15. However, for higher sample sizes (m $\geq$ 50) the sensitivity was pretty similar for both methods. By comparing the trend at skewness values of γ = 1, γ = -1, γ = 0.5 and γ = -0.5, we can clearly see LW-MS performed better across all sample sizes and the trend was pretty similar for all values of skewness. For lower skewness of γ = 0.5 and γ = -0.5 we did observe an asymmetrical trend for both methods though. For the skewness value of γ = 0.5, the sensitivity of the LW-WT became better when the number of subjects reached the range of m = 80 to m = 100. This asymmetry could be possibly arising from the skewness in the contingency tables originating from skewness of the data. We also observed that when the sample size was m ≈ 90, the detection rate of two methods converged at $\approx 100\%$ for larger skewness values of γ = -1 and γ = 1. However, for smaller skewness values of γ = 0.5 and γ = -0.5 the convergence happened later when the sample size was m = 100.

Overall we demonstrated that using LW-MS has the potential to more accurately identify salient functional links between two empirical conditions as compared to conventional methods. We also emphasize that the use of the LW-MS method is not restricted to FC networks but could be also applied to comparisons of other connectivity datasets such as Structural Connectivity (SC) and Effective Connectivity (EC). We are aware that there are other methods like Network Based Statistic (NBS) [Zalesky et al., 2010] which specifically aims to tackle the problem of multiple comparisons via network based approach. LW-MS however does not aim to directly deal with the number of multiple comparisons per se, it is simply aimed to be more *sensitive* to capture the differences. The p values obtained by this method can even be paired with NBS since these methods are aiming to make it easier for us to detect salient links at different steps of the analysis.

2.4.1 Natural Viewing vs Rest

The functional brain links which were found to be significantly different between resting-state and natural viewing condition were right Parahippocampus Gyrus – left Pars Opercularis, right Parahippocampus – left Supramarginal gyrus, right Caudal Anterior Cingulate Cortex – left Superior Parietal Lobule and, right Posterior Cingulate Cortex – left Superior Parietal Lobule. Right Parahippocampal Gyrus has been shown to activate when subjects are viewing passive scenes especially the ones depicting bare spatial layout [Epstein and Kanwisher, 1998, Reilhac et al., 2013, Zeidman et al., 2012]. Its functional connection with left Pars Opercularis shows the binding between higher order visual area and language area. Left Pars Opercularis has also been implicated for motion learning [Fazio et al., 2009, Clerget et al., 2011] hinting at a dual role for the link between right Parahippocampal Gyrus and left Pars Opercularis obtained in this analysis. Another link of right Parahippocampal Gyrus has been found with left Supramarginal Gyrus, which is thought to create communication between perceptual and motor systems [Parker et al., 2005]. It has also been linked with sentex complexity, grammatical errors and other language tasks in auditory domain [Raettig et al., 2010, Friederici et al., 2009, Obleser and Kotz, 2010]. These findings show two functional links which are connecting language and visual areas.

The remaining two links, right Caudal Anterior Cingulate Cortex â left Superior Parietal Lobule and, right Posterior Cingulate Cortex - left Superior Parietal Lobule are well known for their role in attention. Right Caudal Anterior Cingulate Cortex (cACC) has been shown to play an important role in focusing visual attention in the presence of distractions [Weissman et al., 2006]. Its activation has also been observed during auditory Stroop task [Haupt et al., 2009] showing its modality independent role in modulating attention. In resting state imaging, it has been shown to be negatively correlated with Default Mode Network (DMN) and positively correlated with other attention areas like left Superior Parietal Lobule (SPL) [Fox et al., 2005]. Just like cACC, the left SPL has been shown to be important for both auditory and visual attention [Pugh et al., 1996, Shomstein and Yantis, 2006, Corbetta et al., 1993, Szczepanski et al., 2010]. Its anticorrelation with the DMN areas specifically with the right Posterior Cingulate Cortex (PCC) has been repeatedly observed [Fox et al., 2005, Margulies et al., 2007, Clare Kelly et al., 2008]. Specifically the right PCC has been shown to decrease activation in the presence of attention. Taken together, one can suspect that left SPL along with right cACC is activated during the natural viewing since focusing attention is required for this task. However, this outward attention could be the cause of deactivation of right PCC forming a network with left SPL via direct communication and right cACC via an indirect one.

2.5 Conclusion

This study presented a new method to study localized differences between functional brain links by thresholding the correlation using the median, namely LW-MS. With the use of simulations, we showed that it is more powerful than using traditional method of using un-thresholded data and performing non-parametric test. We also showed that the sensitivity of LW-MS and traditional methods are unaffected by skewness of the distribution and LW-MS performs better especially for low sample sizes. We also tested the limits of the method and showed that in case of extremely low sample size (m ≤ 10), both traditional method and our method performed marginally ($\leq 1\%$). Also, there is an inverse relationship between the power of the method and the number of brain functional regions resulting from different parcellations as expected. However the power decreased stepwise unlike for the LW-WT where it decreased gradually. We showed a practical application of LW-MS by using a case-control study aimed to detect differences between resting state and natural viewing conditions. We successfully identified functional brain links binding higher order visual area via right Parahippocampal Gyrus and language areas like left Pars Opercularis and left Supramarginal Gyrus. We also identified functional brain links responsible for modulating attention via DMN area (right PCC) and attention areas like left SPL and right cACC highlighting the underlying role of attention in natural viewing process. We believe that LW-MS will be helpful in exploring local differences of functional brain networks in the future.

Chapter 3

TRACES OF STATISTICAL LEARNING IN THE BRAIN’S FUNCTIONAL CONNECTIVITY AFTER ARTIFICIAL LANGUAGE EXPOSURE

Sengupta P, Burgaleta M, Zamora-López G, Basora A, Sanjuán A, Deco G, et al. Traces of statistical learning in the brain’s functional connectivity after artificial language exposure. Neuropsychologia. 2019 Feb 18;124:246–53. DOI: 10.1016/j.neuropsychologia.2018.12.001

Chapter 4

RESTING STATE NEURAL CORRELATES OF SOCIAL HIERARCHY PERCEPTION: A COMBINED EEG-FMRI STUDY

Pallabi Sengupta, Miguel Burgaleta, Gorka Zamora-López, Hernando Santamaría-García, Gustavo Deco, Nuria Sebastian-Galles

4.1 Abstract

Perceiving social hierarchy is a fundamental step in the social interactions in human lives. Previous studies investigating the underlying neural mechanism of this cognitive process revealed the role played by the sense of self arising from resting state activity. Till date no study has looked directly into this aspect by exploring the role played by intrinsic functional connectivity in driving individual differences in social hierarchy perception. Here we combined resting state fMRI with event-related potentials to reveal resting state neural correlates of social hierarchy perception. We used a previously validated procedure [Santamaría-García et al., 2015] to create simulated hierarchical scenario, where participants played a visual discrimination task either with a high or a low ranking individual. In accordance with previous studies [Santamaría-García et al., 2015], we used the difference in the value of N170 component when participants viewed a superior player and when they viewed an inferior player as an indicator of social hierarchy perception. We investigated significant correlations between this ERP marker and resting state functional couplings revealing links between right Insula and left Parahippocampal Gyrus, as well as, left Superior Frontal Gyrus and left Superior Temporal Sulcus. We conclude that individual differences in the perception of social hierarchy are induced by functional connections binding social and emotional evaluation on the one hand, and mentalizing and automatic face perception on the other.

4.2 Introduction

Humans, non-human primates, and a variety of other species are organized in social dominance hierarchies. Recognizing hierarchical social marks are crucial in regulating group resources, avoiding conflicts, and favouring reproductive success [Rushworth et al., 2013, Cheney and Seyfarth, 1990]. In addition, the social status affects health and well-being of human [Boyce, 2004, Sapolsky, 2004] and non-human primates [Sapolsky, 2004, Sapolsky, 2005]. In humans, perceiving social status in others is an implicit process that affects how an individual experiences one's own social status [Santamaría-García et al., 2015] and modulates different cognitive processes from the most basic perceptual processes [Santamaría-García et al., 2013, Zink et al., 2008] to more cognitive â reflexive and executive processes [Boksem et al., 2012, Santamaría-García et al., 2017]. Hierarchical social cues can be conveyed by implicit sources including face features, voice marks, verbal assignment, or body postures, among others [Karafin et al., 2004, Oosterhof and Todorov, 2008].

Our understanding of the underlying neural mechanism responsible for such social status interaction remains incomplete. In this regard, some brain regions have been consistently identified by task-based functional Magnetic Resonance Imaging (fMRI) studies, namely, Fusiform gyrus, Superior Temporal Gyrus/Sulcus, Amygdala, Intraparietal Sulcus, rostro medial Prefrontal Cortex, Posterior Cingulate Cortex, Insula, and the Ventral Striatum [Chiao et al., 2008, Grill-Spector et al., 2004, Kumaran et al., 2012, Zink et al., 2008]. Extending this knowledge further to neuroanatomy, [Santamaría-García et al., 2015] found individual differences in social hierarchy perception to be modulated by the morphology of a network of cortico-subcortical network consisting of superior temporal sulcus, the right posterior cingulate cortex, the anteroventral temporal lobe, fusiform gyrus, the right insula and, the caudate nucleus. In a similar vein, [Bickart et al., 2012] investigated intrinsic functional connectivity inducing individual differences in social network size of humans, and found the intrinsic connectivity of amygdale to be a key factor in inducing differences in the size and complexity of social network at an individual level. Indeed, individual differences in intrinsic connectivity strength has been reported to predict individual differences in a wide range of cognitive tasks like motor function [Fox and Raichle, 2007], memory [Wang et al., 2010], and executive function [Seeley et al., 2007]. However, intrinsic connectivity modulating individual differences in social hierarchy perception remains to be investigated. The current study is aimed to complete this part of the puzzle, by combining Event Related Potential (ERP) and resting state fMRI (rsfMRI) to investigate individual differences in fine-grained temporal dynamics of hierarchy perception and to explore the rsFC inducing these individual differences. Combination of ERP and MRI has already been employed by multiple studies to connect brain morphology with cognitive abilities [Fjell et al., 2007, Walhovd et al., 2005, Westlye et al., 2009], including social hierarchy perception [Santamaría-García et al., 2015]. Here we have gone one step forward by combining rsfMRI and ERP markers in a similar fashion.

In this study, a simulated social hierarchy was built using a procedure previously used and validated [Zink et al., 2008, Santamaría-García et al., 2015, Santamaría-García et al., 2013]. Participants were shown two simulated players, Superior Player (SP) and Inferior Player (IP) against whom they performed a visual discrimination task. ERPs were recorded while participants watched the faces of their opponents along with explicit marks denoting their status; three stars for the SP and one star for the IP (Figure 4.1). Using the same procedure, [Santamaría-García et al., 2013] reported that participants were faster while performing the visual discrimination task with SP showing modulation of social hierarchy in decision making processes. They also found an effect of social hierarchy in the amplitude of the N170 component, indicating this component as a potential ERP marker signalling social hierarchy perception.

Bolstering these findings, [Santamaría-García et al., 2015] used the difference in the amplitude of N170 when the participants viewed two simulated opponents (superior minus inferior) as an ERP marker signalling social hierarchy perception. This ERP marker, which they denoted as ΔN170 was then used to successfully reveal anatomical correlates driving individual differences in social hierarchy perception. It is of note that the authors also used other ERP components C1 and P1, which were also reported by previous studies to be affected by social hierarchy perception in faces [Santamaría-García et al., 2013]. Unlike ΔN170, the authors failed to find any results using other ERP components, making us also choose ΔN170 for the current analysis.

Here we focused on the association between ΔN170 and rsFCs in a data-driven fashion, by investigating all the functional connections (i.e., link) between parcellated anatomical brain regions. To make the analysis more sensitive, we binarized each and every link using median splitting. This method which we refer to as Link Wise Median Splitting (LW-MS) has been proven to be a sensitive method to detect functional brain links in a case-control scenario (Sengupta et al., in preparation). Furthermore, median splitting has been successfully used in a variety of applications [Kastrati et al., 2011, Kim et al., 2013, MacCallum et al., 2002, McCarthy et al., 2013], showing its utility across different scenarios. Here, we extended the applicability of this method by using it in a study design unlike case-control paradigm. Based on previous literature we hypothesized significant correlation between ΔN170 and links comprising brain areas are reported to be sensitive to perceiving social cues, i.e., fusiform gyrus, parahippocampal gyrus, superior frontal gyrus, superior temporal sulcus, insula, striatum, amygdala, and, parahippocampal gyrus [Kumaran et al., 2012, Mars et al., 2012, Santamaría-García et al., 2015, Zink et al., 2008].

4.3 Methods

Since we followed the exact same procedure as [Santamaría-García et al., 2015], the current section is adapted from the same.

4.3.1 Participants

Twenty-one participants took part in this study. Eleven of them were female and they were all right-handed. They were undergraduate students from Universitat Pompeu Fabra (Spain) in the age range of 18-27 years (23.39 years ± 2.4 years). Participants received 10 Euros per hour and were invited via an open call for participation. None of the participants reported psychiatric or neurological conditions and all of them reported normal visual accuracy. Before partaking in the study, informed consent was obtained from all the participants. The study was approved by the ethics committee of Universitat Pompeu Fabra and it was in compliance the Code of Ethics of the World Medical Association (Declaration of Helsinki). This sample is a subset of the participants included in [Santamaría-García et al., 2013].

4.3.2 Materials and procedure

We utilized a well-used social hierarchical paradigm to create a social hierarchical environment [Santamaría-García et al., 2013, Santamaría-García et al., 2015, Zink et al., 2008]. To initialize the hierarchical setting we used brief samples of profile videos, followed by an interactive game in which participants performed a visual discrimination task in presence of simulated opponents. A schematic for the whole experiment design is depicted in Figure 4.1.

4.3.3 Profile videos

We used eight different videos of ≈ 2 min each showing simulated players' profiles. The simulated profiles were created for different sex (male, female) and hierarchy (high, low status), and were played by four actors (two males, two females, ≈ 25 years old). Each actor followed two scripts in which personal, work, and academic achievements of the characters were reported (the SP reported many successes in the professional, academic, business, and social fields, whereas the IP reported low education, few job opportunities, and social difficulties). Implicit cues indicating social dominance was controlled by avoiding substantial differences in their clothing, posture, facial expressions, and age.

4.3.4 Simulated game

Participants played a visual discrimination task at the same time with one of the two simulated opponents. On average SP was shown, to have better performance than the participant and consistently held a high rank status. On the other hand, IP was shown to perform worse in a similar fashion to have a lower rank. The SP and the IP, previously shown in social videos constantly had a high and low rank in the game phase, respectively. Profiles of both actors (SP and IP) were counterbalanced across participants. In

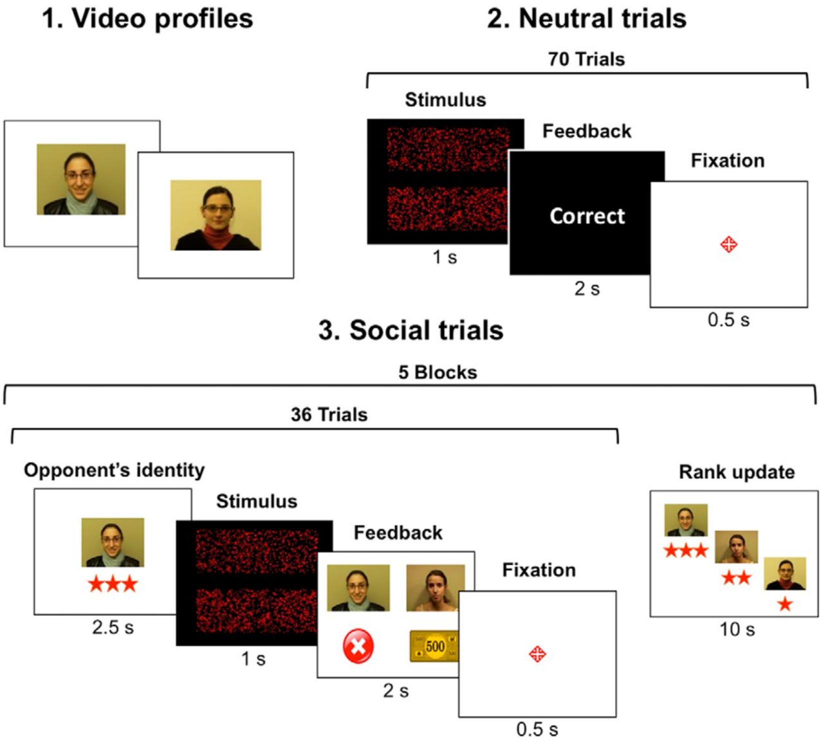


Figure 4.1: Hierarchy game structure. The procedure had three stages: social video profiles (stage 1), neutral trials (2), and social trials (3). During stage 1, two confederates represented the superior and the IP. During stage 2, participants performed 70 trials in a neutral context (here, hierarchical scenario was avoided). During stage 3, participants performed the visual discrimination task while comparing their performance with the simulated players. The figure is relpicated from [Santamaría-García et al., 2015]

each trial, after participants performed the visual task, feedback of their own performance, along with that of the simulated player, were displayed on the screen.

4.3.5 Hierarchical stimulus

A photograph of the simulated opponent was displayed with its corresponding hierarchical status at the beginning of each trial (three stars for SP and one star for IP). The simulated player always maintained a neutral position and the gaze to the front in the photographs.

4.3.6 Visual decision task

We presented two rectangles of red dots on a black background, one at the top of the screen and the other at the bottom. Participants were situated $\approx$ 50 cm in front of a 19-inch screen with an angle of vision of $\approx 35^\circ$. All dots had the same diameter, shape, and brightness. Each rectangle had a different percentage of red dots which were more than 1000 dots in total. The percentage of red dots was complementary between the rectangles (e.g., if one had 30% of the dots, the other had 70%).We displayed screenshots of each rectangle in every trial, with nine levels of dot percentages (44, 46, 48, 49, 51, 52, 54, and 56).

4.3.7 Procedure

We controlled for possible interactions between sex and hierarchy, i.e., male participants played with male-simulated players and female participants with female-simulated players. Participants were informed that they would play visual discrimination game and their performance would be compared with that of two players who had already completed the task and ranked accordingly. Participants were informed about the possibility that their performance could be compared with future subjects.

Subjects were placed in an electrically shielded room located in the Neuroscience Laboratory of the Center for Brain and Cognition (Universitat Pompeu Fabra, Barcelona) where EEG activity was measured. The experiment began right after electrode application. Initial hierarchy was established by displaying a 2 min video of the other players (Fig. 4.1) in the beginning.

Participants performed 70 practice trials where they played the game solo and received feedback after each response. Participants had up to 1s to decide which rectangle contained more red dots using the corresponding lever (up/down) of a joystick. The game began right after training with five blocks of 36 trials (180 total, 90 with each simulated player). In each block which lasted around 5 min, participants played nine consecutive trials with each player twice, followed by presentation of the updated ranking. Participants could rest for up to 2 min between blocks. As mentioned above ranks of the participant were always fixed by manipulating the SP's or IP's behaviour. Each trial lasted $\approx$ 5s and started with a 1s presentation of the opponent's photograph (hierarchical stimulus) with its corresponding ranking. Then, participants performed the visual discrimination task lasting 1s followed by feedback for 2s: pictures of the participant and opponent above, and outcome (a coin meaning correct, an ”X” meaning incorrect or a ”time over” message) below. Both players could win or lose in a trial which ended with the fixation cross for 1s.

4.3.8 EEG/ERP recording

EEGs were recorded from 31 scalp sites. Two bipolar electrodes were placed above and below the participant's left recording eye movements, two electrodes on the mastoids, and a reference electrode on the nose. EEG recordings were digitized at 250 Hz. All electrode impedances were $<$ 3 KOhms. The EEG data were low- and high-pass filtered (30-0.03 Hz). Two different kinds of analyses were used: stimulus-locked and response-locked analysis. In the stimulus-locked analysis, EEG was segmented into 1100 ms epochs ranging from 100 ms before stimulus onset to 1000 ms after onset (visual discrimination task). Before averaging, segments were baseline corrected by subtracting the mean amplitude of the pre-stimulus interval (-100-0 ms). All EEG data were semi automatically screened offline for eye movements, muscle artefacts, electrode drifting, and amplifier blocking wherein segments containing such artefacts were discarded. We calculated the social hierarchy perception of each participant by calculating the difference in the N170 component when the participant viewed the face of SP minus the one when they viewed the face of the IP and denoted this component by ΔN170. This measure has been successfully used before by [Santamaría-García et al., 2015].

4.3.9 Resting State Scans

Participants were instructed to rest with their eyes closed and not to sleep or think about anything in particular. Images were obtained in a GE 1.5 T scanner using a gradient-echo T2*- weighted echoplanar imaging sequence in the axial plane (TR, 2000 ms; TE, 50 ms; matrix, 64×64; voxel size, 3.75×3.75 mm; flip angle, 90°; slice thickness, 4 mm; FOV = 240) and 120 volumes. During audio exposure, fMRI was also acquired, with identical parameters to the rs-fMRI sequence and 106 volumes.

4.3.9.1 Image Preprocessing

Rs-fMRI datasets were processed using the Data Processing Assistant for Resting-State fMRI (DPARSF; [Chao-Gan Y, 2010]). The rs-fMRI preprocessing included the slice-timing correction for interleaved acquisitions using sinc interpolation and resampling with respect to the middle slice in time, head motion correction, spatial normalization to the MNI standard space, and spatial smoothing with an isotropic Gaussian kernel of 4 mm FWHM. Further preprocessing steps included: (1) removing the linear trend in the time series, (2) temporally bandpass filtering (0.01-0.08 Hz) to reduce the effect of low-frequency drift and high-frequency noise [Biswal et al., 1995, Lowe et al., 1998], and (3) controlling the nonneural noise in the seed region time series [Fox et al., 2005]. Several sources of spurious variance were removed from the data through linear regression: six parameters from rigid body correction of head motion, the global mean signal, the white matter signal, and the CSF signal.

4.3.9.2 Functional Connectivity (FC) Matrices

To generate FC matrix for each subject, Pearson's correlation was calculated between time-series of every combination of 90 AAL regions leading to a 90×90 matrix. To transform Pearson's correlation value, r into normally distributed values, Fisher's z-transformation was applied to all the correlation matrices. These matrices represented the underlying network connectivity where the correlation value between i^{th} row and j^{th} column represents the functional link between i^{th} and j^{th} nodes of the network.

We binarized the FC matrices using median splitting. This method that we referred to as Link Wise Median Splitting (LW-MS) has been previously shown to be able to successfully detect salient functional connections in a case-control scenario (Sengupta et al., in preparation). It has also been used in a wide variety of applications from detection of the effect of glycoprotein inhibitors and heparin for myocardial infarction [Kastrati et al., 2011], to study gesture sequences in captive chimpanzees [McCarthy et al., 2013], or to characterize driving behaviour in teenagers using a Bayesian Model [Kim et al., 2013] among other examples [MacCallum et al., 2002], further showing its applicability. In this study we extended its versatility by applying median splitting in a paradigm unlike a case-control design. For this purpose, we calculated the median of all the link values across all subjects. All the links which were below this median value were denoted the value of 0 and all the links above the median was denoted to be 1. For some links the correlation value was ≈ 0.9 across all subjects rendering their new values to be 1. For some links on the other hand the link value was lower than the median across all subjects rendering their new values to be 0. Our interest lied with the links with some variation across subjects which could be correlated with their ΔN170 value.

4.3.10 Statistical Analysis

After binarization, we calculated the correlation between every possible functional brain link and the $\hat{I}$N170 component for each participant using biserial correlation. We selected all the links with uncorrected $p < 0.0001$. We also corrected all the p values for multiple comparisons using FDR [Storey, 2002] and rechecked the corrected p value for the chosen links. Before performing the analysis we checked if all the assumptions for running biserial correlation are satisfied by ΔN170. The normality of ΔN170 was tested using Shapiro-Wilk test while the assumption that continuous variable should have equal variances for each category of the dichotomous variable was tested using Levene's test of equality of variances. Finally, the number of outliers was determined by plotting a boxplot of ΔN170 which came out to be 0. All the analyses were performed in MATLAB, Python and RStudio.

4.4 Results

4.4.1 Functional Brain Links are Linked to ΔN170

Results revealed that two links were significantly correlated after FDR correction (Figure 4.2): 1) right Insula - left Parahippocampal Gyrus and, 2) left Medial Frontal Gyrus - left Superior Temporal Gyrus/Sulcus. The p values as well as the correlation values obtained from the two links were pretty similar (uncorrected p = 6.9504×10^{-4}, r = -0.7419). After correction for multiple comparisons, we obtained the same links with corrected p $\approx$ 0.05. Both links were anticorrelated with ΔN170 component revealing that for better perception of social hierarchy, the correlation between right Insula and left Parahippocampal Gyrus as well as between left Medial Frontal Gyrus and left Superior Temporal Sulcus/Gyrus should decrease. This hinted at the presence of anticorrelations between right Insula and left Parahippocampal Gyrus as well between left Medial Frontal Gyrus and left Superior Temporal Sulcus/Gyrus required for social hierarchy perception.

4.5 Discussion

The current study combined ERPs and resting-state fMRI to determine the resting state neural correlates driving inter-individual differences in social hierarchy perception. The combination of ERPs and resting-state fMRI has been previously used successfully to model top-down attentional processes [Crottaz-Herbette and Menon, 2006], and provided us a unique opportunity to use a fine-grained ERP-based measure to investigate the rsFC driving differences in social hierarchy perception at an individual level. We revealed the role of two resting state functional couplings, one between right Insula and left Parahippocampal Gyrus and the other between left Medial Frontal Gyrus and left Superior Temporal Gyrus inducing individual differences in social hierarchy perception.

One of the regions obtained by our analysis, right Insula (rIn) has been shown to be involved in recognition of contextual social information associated to faces [Eisenberger, 2003] and in categorization of faces according to their learned social status [Eger et al., 2013]. Exhibiting a more general role played by the Insula, [Bzdok et al., 2012] found activation of bilateral Insula among other regions to be involved in social judgments of faces,

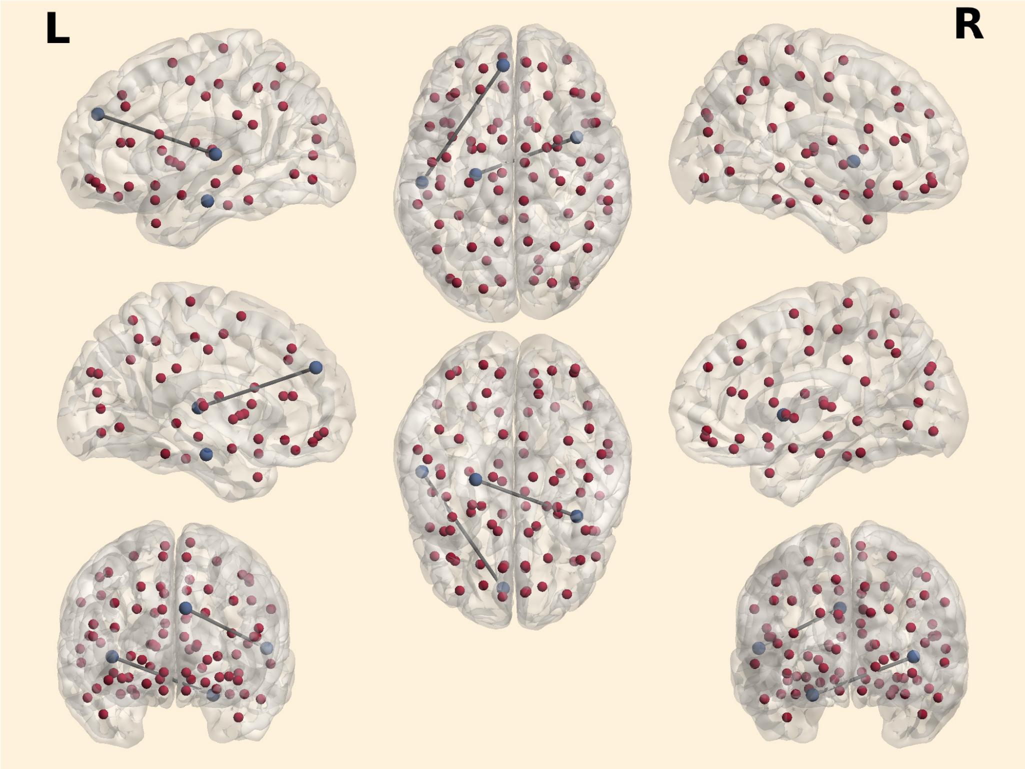


Figure 4.2: Resting state functional brain links between right Insula and left Parahippocampal Gyrus along with left Superior Frontal Medial and left Superior Temporal Sulcus were found to be important. The presence or absence of these links are significantly correlated with social hierarchy perception after correcting for multiple comparisons. We used BrainNet Viewer developed by [Xia et al., 2013] to show the functional brain links.

which is a key step in contextualizing social hierarchy. A more direct evidence of the involvement of rIn in social hierarchy perception comes from [Santamaría-García et al., 2015], who reported the morphology of rIn to be correlated with individual differences in social hierarchy perception. It is important to remember that the involvement of rIn could also arise from an emotional component associated with hierarchy recognition Indeed Insula has been consistently identified as a brain area responsible arousal regulation [Craig and Craig, 2002, Paulus and Frank, 2003, Turk et al., 2004], which a key component of hierarchy recognition [Boyce, 2004, Mehta et al., 2008].

In this study we found that rIn was linked with left Parahippocampal Gyrus (PG). Its role has been reported for emotional evaluation and emotional learning [Lane et al., 1997, Tabert et al., 2001, Trautmann et al., 2009, Winston et al., 2002, Wood et al., 2005]. A more direct evidence of the involvement of left PG in social hierarchy perception comes from the findings of [Zink et al., 2008] who reported differential activation of bilateral PG depending on the status of the opponents. It is also implicated in associated learning suggesting that participants might have adjusted their performance in the task after recognizing the social order and then changing their expectance in that social context [Aminoff et al., 2007]. Its role is well known in Social Anxiety Disorder (SAD), where patients experience fear and anxiety from social situations [Hattingh et al., 2013]. [Hattingh et al., 2013] observed higher activation in left PG in SAD subjects as compared to healthy individuals showing that deactivation of left PG is required for social interactions. This made us speculate that an activation of rIn and deactivation of left PG might be at play during social hierarchy perception leading to an anticorrelation between the two.

Another significant link observed in this study was between the medial part of the Left Superior Frontal Gyrus (SFG), which has been consistently observed to play a role in perceiving 'social' dominance as part of the Prefrontal Cortex [Watanabe and Yamamoto, 2015] and the Left Superior Temporal Sulcus (STS), which has been thought to be part of a distributed neural system for face perception [Haxby et al., 2000]. The medial part of Superior Frontal Gyrus (SFG), has been shown to be involved in differentiating between self and other [Vanderwal et al., 2008] especially for face processing [Zhang et al., 2009a]. Its high activity has been consistently reported in cognitive-affective brain disorders like internet addiction (Yuan et al., 2013), attention deficit hyperactivity disorder [Li et al., 2014a, Yang et al., 2011], depression [Liu et al., 2014, Xu et al., 2014], and anxiety disorders including obsessive-compulsive disorder [Hou et al., 2012] and posttraumatic stress disorder [Yan et al., 2013] showing that for normal social functioning, its activity should decrease.

Left STS is linked to emotional and social cues in faces [Marsh et al., 2009, Mende-siedlecki et al., 2013, Muscatell et al., 2012, Stanley and Adolphs, 2013, Trautmann et al., 2009]. Its activation has also been reported by [Vanderwal et al., 2008] during self vs other referential task, hence implicating STS in wider social processes, especially in distinguishing between self and other. This view is bolstered by its activation while viewing parental faces [Zhai et al., 2016]. Since the current study found status-related differences in the 'face selective' ERP component, which was in turn used as a marker of social hierarchy perception, the involvement of the left STS was unsurprising. This view is consistent with the findings of [Santamaría-García et al., 2015], who reported that that cortical surface area (CSA) of the left STS correlates with ΔN170, ERP marker of social hierarchy perception. This shows that its activation along deactivation of SFG is required for normal social functioning giving rise to an anticorrelation observed in this study.

Taken together, we have observed two rsFCs modulating individual differences in early social status recognition, captured by the N170 component. Even though the corrected p values obtained for both links were at trend (p ≈ 0.05), it is important to remember that we did not pre select the regions, which is quite common in the neuroimaging literature. We believe that a replication with larger sample size will be able to confirm these findings. One of the rsFC obtained in this finding is an anticorrelation between rIn and left PG, binding social and emotional evaluations together. But since PG is also responsible for memory we cannot rule out the possibility that the link between rIn and left PG is to modulate the social evaluation based on memory and one's sense of self arising from that.

Another important link observed in this study was between left SFG, a DMN area, and left STC which might serve as a link between mentalizing and social aspects of face perception. The two links thus can point to the direction of the required basic steps for social hierarchy perception. First, left STC must be activated to comprehend social cues from the faces of the opponents while deactivation of SFG will enable the subjects to distinguish between self and the other. To construct the social hierarchy and put oneself in it, rIn will be activated while left PG will be deactivated leading to a connection between social and emotional evaluation of the situation preparing the subjects to act accordingly. Since the links obtained were in the resting state, the aforementioned scenario shows the possible steps that our brain needs to be ’prepared’ for during rest itself. Indeed correlations between resting state couplings and task networks have been consistently reported [Biswal et al., 1995, Smith et al., 2009], hinting at the ’preparedness’ of our brain. The extent of this ’preparedness’ influences the extent to which we can perceive social cue around us and interact accordingly.

Conclusion

The current study highlighted the importance of the functional coupling between rIn and the left PG along with left SFG and left STS in the resting-state brain for perception of social hierarchy using a combination of rs-fMRI and ERPs. We speculate that the negative correlation between the links and ΔN170 is the result of an anticorrelation emerging from inhibition of left PG and left SFG and activation of rIn and left STS.

Acknowledgements

This research was supported by grants from the European Community’s Seventh Framework Programme (FP7/2007-2013): ERG grant agreement number 323961 (Under Control); the Spanish Ministerio de Economía y Competitividad (PSI2015-66918-P) and the Catalan Government (SGR 2014-1210). Miguel Burgaleta is funded by the Juan de la Cierva Incorporación grant (IJCI-2015- 25056). Gorka Zamora-López has been funded by European Union’s Horizon 2020 research and innovation programme under Grant Agreement No. 720270 (HBP SGA1).

Chapter 5

DISCUSSION

The goal of this thesis was to introduce a method designed to detect salient functional links without a priori or a posteriori selection bias. In Chapter 1, we gave a general introduction of the field of resting state functional connectivity and the importance of looking into local information namely the functional brain links in the resting state brain. We also discussed the various methods available to the researchers to explore salient functional connections in the simplest study design, case-control scenario. The different limitations highlighted in Chapter 1, called for a method free of pre or post selection bias without increasing the complexity of the method. In Chapter 2, we introduced a new method, namely Link Wise Median Splitting (LW-MS) which was aimed to solve these issues raised in Chapter 1. With the aid of simulations, we exhibited that LW-MS is more sensitive than traditional non-parametric methods to true differences in functional connections in a case-control scenario, especially across small sample sizes.

In Chapter 2, we applied LW-MS in a simple case-control study design aimed to reveal functional connections responsible for natural viewing. Unsurprisingly, LW-MS was capable of detecting four functional brain links hinting towards the neural mechanism underlying the complex process of natural viewing. On the other hand, non-parametric method that we referred to as Link Wise Weighted Test (LW-WT) failed to detect any salient link. To further test the capability of LW-MS, we applied it to a more complex study design in Chapter 3, where we aimed to understand the resting state salient functional brain link responsible for statistical learning in the auditory domain. Again, LW-MS was able to detect change in the resting state functional brain link between right Posterior Cingulate Cortex (PCC) and left Superior Parietal Lobule (SPL), after participants listened to auditory stimuli consisting of statistical properties. The control stimulus consisting of similar sounds while devoid of any statistical pattern ensured that the link obtained was solely responsible for statistical learning.

Chapter 4 was aimed to investigate the resting state functional connections inducing inter-individual differences in social hierarchy perception. In this chapter we pushed the limits of LW-MS in terms of study design since we were not interested in group differences but in individual differences. Using LW-MS, we were successful in capturing two functional brain links albeit the significance was at trend level after correcting for multiple comparisons ($p = 0.05$). The low level of significance pointed to the need of testing the LW-MS in a design akin to the one presented in Chapter 4 and adapting it further to detect functional links in a study design aimed to explore individual differences. It is worth noting that traditional parametric method performed much worse in this study design, again highlighting the increased sensitivity of LW-MS independent of the paradigm. The high value of significance, as pointed out later in this Chapter, might be arising from low sample size.

Overall, this thesis highlighted the advantage of using LW-MS in detecting salient functional links in the resting state brain. It is noteworthy that LW-MS does not require any assumption pertaining to the resting state functional connectivity, and therefore, can be used on any connectivity obtained in any imaging modality. In the current thesis, the resting state functional connectivity was calculated using Pearson's pairwise correlation, which is the most common method used in neuroimaging studies. However, LW-MS does not require any assumption pertaining to Pearson's correlation, and henceforth can be used on any of the FC methods mentioned in the Introduction (section 1.2). Therefore, it is safe to claim that LW-MS is quite versatile when it comes to its application across different FC methods and imaging modalities. And its application across different study designs presented in this thesis aimed to have furthered its claim of versatile applicability. However, LW-MS also comes with its own sets of limitations in terms of different parameters and it is important to understand them in detail. Some of these parameters as we will observe in the next section can affect connectivity analysis at both local and global level while others are more affective at a local level. After understanding the limitations of LW-MS and its affects in the different studies presented in this thesis, I will present the information revealed about the resting state brain obtained by the three experiments presented in this thesis. Since, all three experiments presented here explored resting state information, I will attempt to combine all the results and make sense of the underlying resting state neural mechanisms underpinning various cognitive processes.

5.1 Parameters Affecting the Analysis

Understandably, several parameters from the FC matrices or the study design can affect the performance of various analysis methods. In this section, these parameters and their effect will be discussed to provide a much clearer picture of LW-MS. As we will see, these parameters also provide the glimpse of limitations of the method.

5.1.1 Parcellation

Brain parcellation or rather segmentation is a renowned image segmentation problem in computer vision and there are various approaches ranging from edge based approaches [Chan and Vese, 2001] to clustering techniques [Chuang et al., 2006] to graph cuts [Shi and Malik, 2000]. However, segmenting neuroimages especially functional neuroimages brings forth additional challenges. One of the first major challenges faced by researchers trying to segment functional images face is the absence of clear boundaries which are present in anatomical brain images.

A clear example of this phenomenon can be seen with IFG, which can be at least divided into two subdivisions [Cox et al., 2014]. However, the huge variability in the structure itself, along with inconsistencies in the functional divisions, makes the task difficult. Another kind of discrepancy can be observed with DLPFC, which can be further subdivided in different regions [Cox et al., 2014]. The areas giving rise to DLPFC vary quite differently depending on the study. While some studies combine SFG and MFG to label DLPFC (e.g., [Croxson, 2005]), other studies separate SFG and only combine IFG and MFG (e.g., [Prasad et al., 2005]). These inconsistencies make the identification of important functional brain links or activations in a study more difficult to interpret. Moreover, labelling the areas differently can cause minor differences in the results observed leading to more inconsistency in the literature. Another effect of different parcellations is the number of brain regions which often lead to different number of functional connections. Higher number of brain regions often led to higher number of functional connections leading to higher number of multiple comparisons making it more difficult to detect significant functional connections.

To examine the effect of parcellation, in Chapter 2 we simulated different scenarios with different parcellation values from 50 to 150. We simulated difference in a functional connection by sampling 50 participants from two different link distributions with different mean values. As elaborated in Chapter 2, we compared the performance of LW-MS with that of LW-WT and found that LW-MS performed much better than non-parametric methods across different parcellations. Another interesting observation was the step-wise decrease in the performance of LW-MS with increasing parcellation unlike gradual decrease of non-parametric methods. If one extrapolates the trend, it is inevitable that the performance of LW-MS and LW-WT would coincide at a very high parcellation value. But such parcellations, are not used in practice and might lead to further complications of interpretations.

Both Chapters 3 and 4 utilized AAL 90 parcellation, which makes the results easy to interpret. In the case application of Chapter 2, we used Hagmann 66 parcellation which is used extensively by various studies. For both 90 and 66 brain regions, we can clearly observe (Figure 2.4) that the performance of LW-MS is much better than that of LW-WT, reconfirming the advantage of using LW-MS over traditional methods. This observation is bolstered by the findings in Chapters 3 and 4 where LW-WT did indeed fail to identify functional brain links unlike LW-MS.

5.1.2 Number of Participants

Sample size has been consistently shown to play an important role in neuroimaging studies irrespective of the designs as pointed out by various studies [Pajula and Tohka, 2016, Button et al., 2013]. Low sample size is the case for large number of neuroimaging studies especially fMRI studies because of the expensive cost of obtaining each scan. A trivial fact is that large sample size produces more consistent results and higher statistical power [Suckling et al., 2010]. Low power resulting from low sample size can lead to multiple problems like overestimation of the effect size of a true effect or requiring stringent thresholds to find if the effect is there or not [Button et al., 2013]. Moreover, low power will automatically mean that the chance that a study is reporting a true effect is extremely low making it highly unreliable.

These situations only exist for simple case-control scenarios or when groups are present and compared. In the case where only one group is present, a simple technique like Inter Participant Correlation (ISC) is used. In the ISC technique, the time series of the fMRI for a brain region is correlated across different participants [Pajula et al., 2012]. For this technique to work properly, [Pajula and Tohka, 2016] estimated that the studies should at least have 30 participants, which is often not observed in neuroimaging. They reported that the lower limit of having acceptable sample size is 20. If a study has less than 20 participants, their simulation showed disastrous results in terms of reproducibility. They also observed that having more than 30 participants did not improve the scenario much further.

Most of these studies which estimated the ideal sample size however, only considered traditional parametric or non-parametric methods. But as pointed out in Chapter 2, LW-MS is more sensitive than traditional methods. Yet to observe the limitations of LW-MS in terms of sample size, we simulated true differences in link distributions and compared the detection rate across various sample sizes with that of traditional non-parametric method (Chapter 2). As detailed in Chapter 2, the performance of LW-MS was better across different scenarios, except when the number of participants was below 20. However, the performance of both methods was extremely low for this situation, making such low sample sizes undesirable. This is similar to the finding of [Pajula and Tohka, 2016] who suggested that sample size should be between 20 to 30. An important observation was that for LW-WT, which is the statistical test used by neuroimaging studies, the performance was worse than that of LW-MS across all sample sizes, but specifically in the case for smaller sample sizes. This might be one of the reasons that the authors reported the ideal sample size to be 30. In all the data-sets used in this thesis, we had more than 20 participants. Even then, LW-WT failed to capture the salient links across all study designs. For Chapter 4, the number of participants was 21, which is lower than the optimal sample size suggested by [Pajula and Tohka, 2016]. This might be one of the reasons that the p value corresponding to the obtained links was not low enough to pass multiple comparisons corrections. As mentioned in Chapter 4, a replication with higher sample size should be able confirm the findings without pre selection biases.

Finally, I would like to mention that all these limitations about sample size mostly focus on only Type I error, which indicates the number of false positives reported by a study. On the other hand, Type II error remains largely ignored by the neuroscience community [Lieberman and Cunningham, 2009]. Ironically (or non-ironically), both these errors could be limited by larger sample sizes, which is often not possible because of high costs of neuroimaging. A possible solution to this problem is collaborative work instead of individual studies. This view has indeed been suggested by multiple studies [Button et al., 2013, David et al., 2013]. In fact, replication studies with large number of participants would be taken more seriously. This is due to the fact that negative results cannot be explained away by low power, battling the problem of publication bias since these results would most likely have to be published.

I would also like to point out, that one of the major factor that is causing low power for most of the true effects reported is publication bias. This bias works at multiple levels, where at a higher level only studies having positive results are published. At a lower level, labs are often forced to focus only on obtaining positive results to publish. Another level is added to this bias, when replication studies especially with negative results are not published often. This bias, as one can imagine, leads to considerable amount of bias regarding the power of the effects. Due to the fact that, only positive results are published, the true effect sizes must be considerable low as compared to the ones reported in individual studies and even meta-analyses. This brings forth two ideas to address the issues of low power often reported in neuroscience. First, more collaborative works should be performed to increase the sample size. Second, negative studies especially with large sample sizes should also be published for us to be able to estimate true effect-sizes.

5.1.3 Study Design

Even though not explicitly mentioned before, study design is an important part of neuroimaging analysis. The statistical tests would be different depending on the study design, as well as the interpretation. To illustrate further, let me give an example where the resting state FC is compared between two conditions where one set of participants viewed a simulated social ranking based on gender while other set of participants viewed a simulated social ranking based on race. To compare the extent of changes induced by the two different social conditioning will utilize Student's t test or Mann-Whitney Test. If the study, however, focused on the individual differences in extent of change in the resting state FC induced by the simulated social ranking based on gender, Pearson's correlation or Spearman's correlation will be employed.

The functional connections obtained in both studies must be playing roles in perceiving social hierarchy solely based on one's appearance. However, their roles and importance might be different depending on the case. The FCs detected by the first study will point to the domain specific mechanisms while the ones detected by the second study will reveal a combination of both domain general as well as domain specific mechanisms. It is very interesting to observe the two very different types of information obtained by the two studies and the very different types of statistical methods that had to be utilized to obtain the information.

In a similar fashion, the methods used for different study designs are also different. The most important difference in the methods is often driven by the questions asked by the study and therefore, the research field. Having said, it is apparent that a lot of analysis methods are used by multiple fields. Some of the most famous examples of such crossovers are graph theoretical techniques [Achard et al., 2006] and to a certain extent Network Based Statistics [Zalesky et al., 2010]. As detailed in the Introduction (section 1.2.2.1), graph theoretical techniques are basically used to explore topographical properties of the communication patterns in the brain. This technique has been 'brought over' from social studies, where the network formed by social interactions is investigated. The Network Based Statistics is the use of network based clustering approaches aimed to address multiple comparisons in exploring functional connections.

For both crossovers, the assumptions and the questions, especially the questions asked by the methods in both fields are quite similar. For the case of graph theory, its application in both social science and neuroscience, gives the similar information. To give a specific example of this similarity, we can look into the investigation of terrorism networks, which are quite important to understand. For this network, important information is held by the person who is a key hub in the network. If this terrorist can be identified, a lot could be learnt about the terrorist network in question among other things. Similarly, key information about the resting state brain network could be obtained by identifying the key hubs in the brain network. In case, of Network Based Statistics, clustering techniques on networks has been in neuroscience itself [Nichols and Holmes, 2002]. The current thesis itself demonstrated the utility of median splitting which is used in other fields showing another crossover in neuroscience.

These crossovers show that the same method can be used to investigate a wide variety of studies. The method presented in this thesis does precisely the same. Even though, in Chapter 2, we only showed better performance of LW-MS in a case-control scenario, different applications presented in this thesis, shows the applicability of LW-MS across different studies. In Chapter 2, the application is a classic case-control study, where LW-MS successfully detected three functional connections. In Chapter 3, the study design involved two groups, with two resting state scans obtained from each group, which is more complex than the case-control study. In Chapter 4, the study design involved only one group and a combination of Event Related Potential and resting state FC to determine functional brain links responsible for social hierarchy perception. The different designs used in this thesis, shows the versatility of LW-MS.

Looking through the different parameters that can affect analysis methods to detect salient functional brain links, it is quite apparent that the method introduced in this thesis is quite useful. A major advantage of using Link Wise Median Split, that was not mentioned before is the limit over type I error. As apparent from Chapter 2, irrespective of the parcellation or sample size, in the absence of true differences, the detection rate for both LW-MS and non-parametric method becomes 0%. The absence of any type I error is quite unnerving given that it must come at a price of higher type II error.

As mentioned in Chapter 2, the absence of any type I error comes from the use of Bonferroni's correction. Even though the true difference is only simulated in one functional link, in all the simulations we are correcting for all the possible functional connections. Even when the number of brain regions is only 50, the number of brain connections are (50 2) = 1225, leading to more than 1000 multiple comparisons. Considering that the number of simulations would still lead to 5% error rate, the error rate detected after Bonferroni's correction would be $\approx 0.0041\%$. As mentioned earlier, even though this would mean extremely negligible chances of finding false positives, restrictive corrections for multiple comparisons is actually making us miss a lot of salient links with true effect due to higher type II errors.

In the current thesis, our only aim was to detect salient links free of any a priori or a posteriori selection bias. For this purpose, we used LW-MS on resting state for three different stimuli revealing crucial information about the functional connections that change in the resting state itself. In the application of Chapter 2, we compared resting state FC with FC obtained during natural viewing. Using LW-MS, we identified three functional brain links encompassing language, visual, auditory and attention areas. In Chapter 3, we compared two resting states obtained after auditory stimuli pertaining to either statistical learning or random audio stream after controlling for the baseline obtained from resting state before the stimuli. Using LW-MS, we observed one functional brain link between right PCC and left SPL, showing the effect of working memory and attention.

In Chapter 4, we correlated functional brain link with Event Related Potential indicating the extent of social hierarchy perception. Using LW-MS at a global level, using the median of all the functional connections across all participants, we observed two functional connections, one between right Insula and left Parahippocampal Gyrus, and the other between left Superior Frontal Medial Lobe and left Superior Temporal Sulcus. These links showed the involvement of emotional perception, facial perception, memory and, self perception. The link between right PCC and left SPL has been observed in both Chapters 2 and 3, even though the studies addressed very different cognitive processes. In Chapter 2, the application aimed to understand natural viewing, while in Chapter 3 the project aimed to understand statistical learning in the auditory domain. The detection of the same brain link in two very distinct processes reveals interesting information about resting state as we will see in detail in the next section.

5.2 The Resting State Brain: What did we learn?

This section is aimed to understand the information revealed by the three experiments presented in this thesis. As mentioned above, Chapter 4 was aimed to understand the intrinsic functional connectivity inducing individual differences in social hierarchy perception. Even though, the links obtained by performing LW-MS did not pass FDR test, they were still significant after chance level without doing any pre selection biases. Of considerable interest is the link between right PCC and left SPL, which was obtained in both Chapters 2 and 3 aimed to understand two different cognitive processes with diverse study designs. So let us first focus on this link and try to understand its involvement in natural viewing (Chapter 2) and statistical learning in auditory domain (Chapter 3).

To understand the role played by the link between left SPL and right PCC, we should first understand the roles played by the two regions separately. The right PCC is a major 'hub' of DMN, partially because of the anatomical properties that it possesses [Hagmann et al., 2008]. As elaborated in the Introduction (section 1.1), the DMN is a network that is 'active' during rest and often deactivates during task performances. As expected, the deactivation of the right PCC has been observed in various tasks including visual discrimination, working memory, among others [Leech and Sharp, 2014, Clare Kelly et al., 2008].

Left SPL on the other hand, is most widely known for its involvement in the fronto-parietal attention network, which is part of the DAN [Corbetta et al., 2008]. Moreover, it is also part of executive control system [Duncan, 2010] and working memory [Linden, 2007]. The functional connection between DAN and DMN, as you might remember from the Introduction (section 1.1), is arguably one of the most well-known functional brain link that has been reported in neuroscientific literature [Buckner et al., 2009]. The 'anticorrelation' between these two networks, forming the functional connection between right PCC and left SPL, has aLW-MSys been associated with attention. This anticorrelation has been questioned by [Murphy et al., 2009] who showed that global signal regression would lead to the presence of false anticorrelations. In this thesis, the data-set used in Chapter 3 had global signal regression as one of the preprocessing steps, while the one in Chapter 2 did not. Since both studies detected the same link, I do not think that global signal regression played a role in their detection. This also cements the importance of the link between DMN and DAN, which is in line with the findings of [Fox et al., 2013].

The two studies in which this link has been detected involved Statistical Learning (Chapter 3) and Natural Viewing (Chapter 2). In Chapter 2, natural viewing was explored by showing the participants a movie, and then comparing the FC obtained during natural viewing and resting state FC. Watching a movie, involves auditory and visual stimuli along with attention demands. This point to the possible roles played by the communication between right PCC and left SPL, involving visual and auditory attention. Along with the involvement of attention, this link also hints at the possibility of working memory.

The involvement of working memory arguably can also be observed in Chapter 3, which was aimed to explore the neural underpinnings of Statistical Learning. In Chapter 3, we investigated statistical learning in the auditory domain and left SPL has been mostly implicated only in the visual domain. However, its implication has also been reported in the auditory attention, showing its domain general role. Since, we told the participants prior to the experiment, that they might be listening to 'alien language'; we think that working memory and executive role of the attention might be at play here. Participants must be expecting 'language' stimuli with statistical regularities and voluntarily allocated attention to the audio stream. Since the audio stream with 'artificial language' (for more details see Chapter 2 Methods section), does contain statistical regularities, the working memory must have been activated. This in turn would lead to major changes between the two conditions as observed.

One might also think that since watching a movie will involve language and will lead to the same involvement of statistical learning as observed in Chapter 2, maybe the link between right PCC and left SPL is just signifying the role of SL in natural viewing. However, we should remember the multiple roles like visual attention and executive attention control played by this link. We should also remember that our brain is a highly efficient organ, where a simple function can recruit a set of functional brain links to be more efficient or a more complex function can recruit one brain link to perform multiple functions. This again reminds me, of the one-to-one mapping that we often have of the neural mechanisms, which is most likely not true.

Another possibility that might be at play here is the simultaneous involvement of top-down as well as bottom-up attention systems. This is assuredly true in the application case study in Chapter 2, since participants would employ bottom-up system, when they received the auditory and visual stimuli. Even if they were not told prior to the experiment about the stimuli, they would also have to employ top-down attention system to comprehend the 'story' behind the movie. In Chapter 3, as well one can suspect the involvement of both attention systems, where participants would first employ top down system expecting to decipher the 'alien' language. They would also have to utilize bottom-up attention after the employment of auditory stimuli. Both these situations are equally likely, and since they both activate and deactivate the same brain regions [Katsuki and Constantinidis, 2014], namely right PCC and left SPL, it is not possible to choose one of the two explanations.

We observed the involvement of attention in one form or the other in both tasks, and we observed the employment of the same brain link between right PCC and left SPL in both projects. This observation might make one think that whenever attention is involved, this brain link must be involved. Indeed the involvement of right PCC also gives the same idea, since it must deactivate for the attention system to start working and this link might as well be the first link to 'start' the process. We note that this might not be the case, and all the links possibly involved in attention might start working together. However, the extent of its role in attention cannot be denied in light of its detection even after performing stringent multiple comparisons correction in two very different scenarios.

But to think of this link as the 'attention' link will be a grave mistake. It has been shown that attention could be divided into two distinct categories namely 'external' and 'internal' [Jack et al., 2013]. In fact this distinction has been brought forth by William James himself, who described one type of attention to be passive, reflexive, involuntary, while the other to be active and voluntary [James, 1890]. Internal attention, which is mostly passive, is focused on tasks that involve the sense of 'self' and hence mostly social tasks. External attention on the other hand is more active and is utilized in tasks that has nothing to do with the idea of self, like a mechanical task or statistical learning. [Jack et al., 2013] presented two attention demanding tasks either in the form of reading a text or watching a movie either involving social condition or involving mechanical condition. They found that social task invoked DMN regions while mechanical task invoked DAN regions, showing that even attention tasks can employ DMN areas as long as the task involves social stimuli.

This brings forth a new explanation of the resting state brain, which instead of being understood as just a baseline, should be looked as a 'self-aware' organ. Indeed, it has been proposed that the DMN is likely observed during social tasks because during ’rest’, our brain is involved in self-related thoughts [Mars et al., 2012] This view can be further supported by the findings presented in Chapter 4, where we found the involvement of social areas like STS, SFG, parahippocampal gyrus and the insula even in the resting state brain. In fact according to our finding, the links reported between these regions, correlated with their social hierarchy perception, showing further that our brain at rest is involved in self-referencing. Therefore, I urge us to shift our focus of trying to divide the two anticorrelated states of our brain not in terms of tasks, and more in terms of the type of tasks.

5.3 Concluding Remarks

Understanding the functional connections in the human brain remains to be a major challenge in the neuroimaging literature. Even though, comprehending their involvement in different cognitive processes provides unique information about the underlying neural mechanism, the sheer number of functional connections to look through makes this an extremely difficult feat. To bypass this challenge, various methods exist from pre selecting the brain links to clustering techniques. However, most methods suffer from pre or post selection bias. The avoidance of these biases come at a cost of high complexity making it more difficult to use the method and also more difficult to interpret the results.

In this thesis, we introduced a new method, namely Link Wise Median Splitting (LW-MS), which addresses these issues by using median splitting. Median splitting has successfully been used previously in other fields like consumer psychology. The contribution of this thesis, therefore, is to show its usage in understanding functional connections. With the aid of various simulations, we have shown its advantage over the use of traditional non-parametric methods. We have also applied the method to three different study designs exploring three different cognitive processes, which further proves its usefulness. Unsurprisingly, LW-MS has successfully identified salient brain links in all three studies unlike its non-thresholded counterpart.

In sum, we claim Link Wise Median Splitting to be a useful method to explore functional connectivity without worrying about complexity, selection bias or error prone results. We hope that in the future more studies will use this method to reveal crucial neural mechanisms.

Bibliography

[Achard et al.,] Achard, S., Salvador, R., Whitcher, B., Sucklig, J., and Bullmore, E. A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs. *Journal of Neuroscience*, 26(1):63–72.

[Achard et al., 2006] Achard, S., Salvador, R., Whitcher, B., Sucklig, J., and Bullmore, E. (2006). A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs. *Journal of Neuroscience*, 26(1):63–72.

[Albert et al., 2009] Albert, N. B., Robertson, E. M., and Miall, R. C. (2009). The Resting Human Brain and Motor Learning. *Current Biology*, 19(12):1023–1027.

[Alexander-Bloch et al., 2013] Alexander-Bloch, A., Giedd, J. N., and Bullmore, E. (2013). Imaging structural co-variance between human brain regions. *Nature Reviews Neuroscience*, 14(5):322–336.

[Aminoff et al., 2007] Aminoff, E., Gronau, N., and Bar, M. (2007). The parahippocampal cortex mediates spatial and nonspatial associations. *Cerebral Cortex*, 17(7):1493–1503.

[Anand et al., 2005] Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V. P., Kalnin, A., and Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. *Biological Psychiatry*, 57(10):1079–1088.

[Andrews-Hanna, 2012] Andrews-Hanna, J. R. (2012). The Brain's Default Network and Its Adaptive Role in Internal Mentation. *The Neuroscientist*, 18(3):251–270.

[Aslin et al., 1998] Aslin, R. N., Saffran, J. R., and Newport, E. L. (1998). Computation of Conditional Probability Statistics by 8-Month-Old Infants. *Psychological Science*, 9(4):321–324.

[Badhwar et al., 2017] Badhwar, A., Tam, A., Dansereau, C., Orban, P., Hoffstaedter, F., and Bellec, P. (2017). Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 8:73–85.

[Baldassarre et al., 2012] Baldassarre, A., Lewis, C. M., Committeri, G., Snyder, A. Z., Romani, G. L., and Corbetta, M. (2012). Individual variability in functional connectivity predicts performance of a perceptual task. *Proceedings of the National Academy of Sciences of the United States of America*, 109(9):3516–21.

[Bassett and Bullmore, 2006] Bassett, D. S. and Bullmore, E. (2006). Small-World Brain Networks. *The Neuroscientist*, 12(6):512–523.

[Bassett et al., 2009] Bassett, D. S., Bullmore, E. T., Meyer-Lindenberg, A., Apud, J. A., Weinberger, D. R., and Coppola, R. (2009). Cognitive fitness of cost-efficient brain functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 106(28):11747–52.

[Bastos and Schoffelen, 2015] Bastos, A. M. and Schoffelen, J.-M. (2015). A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls. *Frontiers in systems neuroscience*, 9(January):175.

[Beckmann et al., 2005] Beckmann, C. F., DeLuca, M., Devlin, J. T., and Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society*, 360(1457):1001–1013.

[Berker, 1986] Berker, E. A. (1986). Translation of Broca's 1865 Report.

[Bickart et al., 2012] Bickart, K. C., Hollenbeck, M. C., Barrett, L. F., and Dickerson, B. C. (2012). Intrinsic Amygdala-Cortical Functional Connectivity Predicts Social Network Size in Humans. *Journal of Neuroscience*, 32(42):14729–14741.

[Bishop and Miller, 2009] Bishop, C. W. and Miller, L. M. (2009). A multisensory cortical network for understanding speech in noise. *Journal of Cognitive Neuroscience*, 21(9):1790–1805.

[Biswal et al., 1995] Biswal, B., Zerrin Yetkin, F., Haughton, V. M., and Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo???planar mri. *Magnetic Resonance in Medicine*, 34(4):537–541.

[Biswal, 2012] Biswal, B. B. (2012). Resting state fMRI: A personal history.

[Biswal et al., 2010] Biswal, B. B., Mennes, M., Zuo, X.-N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A.-M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kotter, R., Li, S.-J., Lin, C.-P., Lowe, M. J., Mackay, C., Madden, D. J., Madsen, K. H., Margulies, D. S., Mayberg, H. S., McMahon, K., Monk, C. S., Mostofsky, S. H., Nagel, B. J., Pekar, J. J., Peltier, S. J., Petersen, S. E., Riedl, V., Rombouts, S. A. R. B., Rypma, B., Schlaggar, B. L., Schmidt, S., Seidler, R. D., Siegle, G. J., Sorg, C., Teng, G.-J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X.-C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y.-F., Zhang, H.-Y., Castellanos, F. X., and Milham, M. P. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences*, 107(10):4734–4739.

[Bo et al., 2011] Bo, J., Jennett, S., and Seidler, R. D. (2011). Working memory capacity correlates with implicit serial reaction time task performance. *Experimental Brain Research*, 214(1):73–81.

[Bo et al., 2012] Bo, J., Jennett, S., and Seidler, R. D. (2012). Differential working memory correlates for implicit sequence performance in young and older adults. *Experimental Brain Research*, 221(4):467–477.

[Boksem et al., 2012] Boksem, M. A., Kostermans, E., Milivojevic, B., and De cremer, D. (2012). Social status determines how we monitor and evaluate our performance. *Social Cognitive and Affective Neuroscience*, 7(3):304–313.

[Boly et al., 2008] Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., Lancellotti, P., Luxen, A., Lamy, M., Moonen, G., Maquet, P., and Laureys, S. (2008). Perception of pain in the minimally conscious state with PET activation: an observational study. *The Lancet Neurology*, 7(11):1013–1020.

[Bonnelle et al., 2012] Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., and Sharp, D. J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sciences*, 109(12):4690–4695.

[Bonnelle et al., 2011] Bonnelle, V., Leech, R., Kinnunen, K. M., Ham, T. E., Beckmann, C. F., De Boissezon, X., Greenwood, R. J., and Sharp, D. J. (2011). Default Mode Network Connectivity Predicts Sustained Attention Deficits after Traumatic Brain Injury. *Journal of Neuroscience*, 31(38):13442–13451.

[Boyce, 2004] Boyce, W. T. (2004). Social stratification, health, and violence in the very young. *Annals of the New York Academy of Sciences*, 1036:47–68.

[Brady et al., 2008] Brady, T. F., Konkle, T., Alvarez, G. A., and Oliva, A. (2008). Visual long-term memory has a massive storage capacity for object details. *Proceedings of the National Academy of Sciences*, 105(38):14325–14329.

[Brewer et al., 2013] Brewer, J. A., Garrison, K. A., and Whitfield-Gabrieli, S. (2013). What about the "self" is processed in the posterior cingulate cortex? *Frontiers in Human Neuroscience*, 7(October):Article 647.

[Britz et al., 2010] Britz, J., Van De Ville, D., and Michel, C. M. (2010). BOLD correlates of EEG topography reveal rapid resting-state network dynamics. *NeuroImage*, 52(4):1162–1170.

[Brown et al., 2005] Brown, T. T., Lugar, H. M., Coalson, R. S., Miezin, F. M., Petersen, S. E., and Schlaggar, B. L. (2005). Developmental changes in human cerebral functional organization for word generation. *Cerebral Cortex*, 15(3):275–290.

[Buckner, 2013] Buckner, R. L. (2013). The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging.

[Buckner et al., 2009] Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., Andrews-Hanna, J. R., Sperling, R. A., and Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci*, 29(6):1860–1873.

[Button et al., 2013] Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., and Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, 14(5):365–376.

[Bzdok et al., 2012] Bzdok, D., Langner, R., Hoffstaedter, F., Turetsky, B. I., Zilles, K., and Eickhoff, S. B. (2012). The modular neuroarchitecture of social judgments on faces. *Cerebral Cortex*, 22(4):951–961.

[Cao et al., 2016] Cao, J., Chen, X., Chen, J., Ai, M., Gan, Y., Wang, W., Lv, Z., Zhang, S., Zhang, S., Wang, S., Kuang, L., and Fang, W. (2016). Resting-state functional MRI of abnormal baseline brain activity in young depressed patients with and without suicidal behavior. *Journal of Affective Disorders*, 205:252–263.

[Cao et al., 2006] Cao, Q., Zang, Y., Sun, L., Sui, M., Long, X., Zou, Q., and Wang, Y. (2006). Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study. *Neuroreport*, 17(10):1033–1036.

[Castellanos et al., 2008] Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghaffari, M., Kirsch, A., Shaw, D., Shehzad, Z., Di Martino, A., Biswal, B., Sonuga-Barke, E. J. S., Rotrosen, J., Adler, L. A., and Milham, M. P. (2008). Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, 63(3):332–337.

[Castellazzi et al., 2014] Castellazzi, G., Palesi, F., Casali, S., Vitali, P., Wheeler-Kingshott, C. A., Sinforiani, E., and D'Angelo, E. (2014). A comprehensive assessment of resting state networks: Bidirectional modification of functional integrity in cerebro-cerebellar networks in dementia. *Frontiers in Neuroscience*, 8(8 JUL):223.

[Cera et al., 2014] Cera, N., Tartaro, A., and Sensi, S. L. (2014). Modafinil alters intrinsic functional connectivity of the right posterior insula: A pharmacological resting state fMRI study. *PLoS ONE*, 9(9):e107145.

[Chai et al., 2016] Chai, X. J., Berken, J. A., Barbeau, E. B., Soles, J., Callahan, M., Chen, J.-K., and Klein, D. (2016). Intrinsic Functional Connectivity in the Adult Brain and Success in Second-Language Learning. *Journal of Neuroscience*, 36(3):755–761.

[Chan and Vese, 2001] Chan, T. F. and Vese, L. A. (2001). Active contours without edges. *IEEE Transactions on Image Processing*, 10(2):266–277.

[Chao-Gan Y, 2010] Chao-Gan Y, Y.-F. Z. (2010). DPARSF: a MATLAB toolbox for âpipelineâ data analysis of resting-state fMRI. *Frontiers in System Neuroscience*, 4:13.

[Cheney and Seyfarth, 1990] Cheney, D. L. and Seyfarth, R. M. (1990). *How monkeys see the world : inside the mind of another species*. University of Chicago Press.

[Chiao et al., 2008] Chiao, J. Y., Adams, R. B., Tse, P. U., Lowenthal, L., Richeson, J. A., and Ambady, N. (2008). Knowing Who's Boss: fMRI and ERP Investigations of Social Dominance Perception. *Group processes & intergroup relations : GPIR*, 11(2):201–214.

[Chou et al., 2006] Chou, T. L., Booth, J. R., Burman, D. D., Bitan, T., Bigio, J. D., Lu, D., and Cone, N. E. (2006). Developmental changes in the neural correlates of semantic processing. *Neuroimage*, 29(4):1141–1149.

[Christoff et al., 2009] Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., and Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences*, 106(21):8719–8724.

[Chuang et al., 2006] Chuang, K.-S., Tzeng, H.-L., Chen, S., Wu, J., and Chen, T.-J. (2006). Fuzzy c-means clustering with spatial information for image segmentation. *Computerized Medical Imaging and Graphics*, 30(1):9–15.

[Clare Kelly et al., 2008] Clare Kelly, A. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., and Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage*, 39(1):527–537.

[Clarke and Sokoloff, 1999] Clarke, D. D. and Sokoloff, L. (1999). Circulation and energy metabolism in the brain. In *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, pages 637–669.

[Clerget et al., 2011] Clerget, E., Badets, A., Duqué, J., and Olivier, E. (2011). Role of Broca's area in motor sequence programming. *NeuroReport*, 22(18):965–969.

[Colby, 2009] Colby, C. L. (2009). *Spatial Cognition*, volume LNCS 1404.

[Cole et al., 2014] Cole, M. W., Bassett, D. S., Power, J. D., Braver, T. S., and Petersen, S. E. (2014). Intrinsic and task-evoked network architectures of the human brain. *Neuron*, 83(1):238–251.

[Cole and Schneider, 2007] Cole, M. W. and Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, 37(1):343–360.

[Conway and Christiansen, 2006] Conway, C. M. and Christiansen, M. H. (2006). Statistical Learning Within and Across Modalities : Abstract versus Stimulus-Specific Representations. *Psychological science*, 17(10):905–912.

[Corbetta et al., 1993] Corbetta, M., Miezin, F. M., Shulman, G. L., and Petersen, S. E. (1993). A PET study of visuospatial attention. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 13(3):1202–26.

[Corbetta et al., 2008] Corbetta, M., Patel, G., and Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind.

[Corbetta and Shulman, 2002] Corbetta, M. and Shulman, G. L. (2002). CONTROL OF GOAL-DIRECTED AND STIMULUS-DRIVEN ATTENTION IN THE BRAIN. *Nature Reviews Neuroscience*, 3(3):215–229.

[Cordes et al., 2002] Cordes, D., Haughton, V., Carew, J. D., Arfanakis, K., and Maravilla, K. (2002). Hierarchical clustering to measure connectivity in fMRI resting-state data. *Magnetic Resonance Imaging*, 20(4):305–317.

[Cox et al., 2014] Cox, S. R., Ferguson, K. J., Royle, N. A., Shenkin, S. D., MacPherson, S. E., MacLullich, A. M. J., Deary, I. J., and Wardlaw, J. M. (2014). A systematic review of brain frontal lobe parcellation techniques in magnetic resonance imaging. *Brain Structure and Function*, 219(1):1–22.

[Craig and Craig, 2002] Craig, A. D. and Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews. Neuroscience*, 3(8):655–666.

[Crone et al., 2011] Crone, J. S., Ladurner, G., Höller, Y., Golaszewski, S., Trinka, E., and Kronbichler, M. (2011). Deactivation of the default mode network as a marker of impaired consciousness: An fmri study. *PLoS ONE*, 6(10):e26373.

[Crottaz-Herbette and Menon, 2006] Crottaz-Herbette, S. and Menon, V. (2006). Where and When the Anterior Cingulate Cortex Modulates Attentional Response: Combined fMRI and ERP Evidence. *Journal of Cognitive Neuroscience*, 18(5):766–780.

[Croxson, 2005] Croxson, P. L. (2005). Quantitative Investigation of Connections of the Prefrontal Cortex in the Human and Macaque using Probabilistic Diffusion Tractography. *Journal of Neuroscience*, 25(39):8854–8866.

[Cunillera et al., 2009] Cunillera, T., Càmara, E., Toro, J. M., Marco-Pallares, J., Sebastián-Galles, N., Ortiz, H., Pujol, J., and Rodríguez-Fornells, A. (2009). Time course and functional neuroanatomy of speech segmentation in adults. *NeuroImage*, 48(3):541–553.

[Ćurčić-Blake et al., 2015] Ćurčić-Blake, B., van der Meer, L., Pijnenborg, G. H., David, A. S., and Aleman, A. (2015). Insight and psychosis: Functional and anatomical brain connectivity and self-reflection in Schizophrenia. *Human Brain Mapping*, 36(12):4859–4868.

[Damoiseaux et al., 2008] Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J. S., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., and Rombouts, S. A. R. B.

(2008). Reduced resting-state brain activity in the ”default network” in normal aging. *Cerebral Cortex*, 18(8):1856–1864.

[Damoiseaux et al., 2006] Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., and Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, 103(37):13848–13853.

[D'Argembeau, 2013] D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: the valuation hypothesis. *Frontiers in human neuroscience*, 7(July):372.

[Daubechies et al., 2009] Daubechies, I., Roussos, E., Takerkart, S., Benharrosh, M., Golden, C., D'Ardenne, K., Richter, W., Cohen, J. D., and Haxby, J. (2009). Independent component analysis for brain fMRI does not select for independence. *Proceedings of the National Academy of Sciences of the United States of America*, 106(26):10415–10422.

[David et al., 2013] David, S. P., Ware, J. J., Chu, I. M., Loftus, P. D., Fusar-Poli, P., Radua, J., Munafò, M. R., and Ioannidis, J. P. (2013). Potential Reporting Bias in fMRI Studies of the Brain. *PLoS ONE*, 8(7).

[De Havas et al., 2012] De Havas, J. A., Parimal, S., Soon, C. S., and Chee, M. W. L. (2012). Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. *NeuroImage*, 59(2):1745–1751.

[De Luca et al., 2005] De Luca, M., Smith, S., De Stefano, N., Federico, A., and Matthews, P. M. (2005). Blood oxygenation level dependent contrast resting state networks are relevant to functional activity in the neocortical sensorimotor system. *Experimental Brain Research*, 167(4):587–594.

[de Pasquale et al., 2010] de Pasquale, F., Della Penna, S., Snyder, A. Z., Lewis, C., Mantini, D., Marzetti, L., Belardinelli, P., Ciancetta, L., Pizzella, V., Romani, G. L., and Corbetta, M. (2010). Temporal dynamics of spontaneous MEG activity in brain networks. *Proceedings of the National Academy of Sciences of the United States of America*, 107(13):6040–6045.

[Demirakca et al., 2016] Demirakca, T., Cardinale, V., Dehn, S., Ruf, M., and Ende, G. (2016). The exercising brain: Changes in functional connectivity induced by an integrated multimodal cognitive and whole-body coordination training. *Neural Plasticity*, 2016:1–11.

[Deng et al., 2016] Deng, Z., Chandrasekaran, B., Wang, S., and Wong, P. C. (2016). Resting-state low-frequency fluctuations reflect individual differences in spoken language learning. *Cortex*, 76:63–78.

[Di Martino et al., 2008] Di Martino, A., Scheres, A., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Shehzad, Z., Biswal, B., Walters, J. R., Castellanos, F. X., and Milham, M. P. (2008). Functional connectivity of human striatum: a resting state FMRI study. *Cerebral cortex (New York, N.Y. : 1991)*, 18(12):2735–47.

[Dichter et al., 2014] Dichter, G. S., Gibbs, D., and Smoski, M. J. (2014). A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder.

[Duncan, 2010] Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour.

[Dutoit et al., 1996] Dutoit, T., Pagel, V., Pierret, N., Bataille, F., and Vrecken, O. V. D. (1996). The MBROLA project: towards a set of high quality speech\nsynthesizers free of use for non commercial purposes. *Proceeding of Fourth International Conference on Spoken Language Processing. ICSLP '96*, 3:2–5.

[Eckert et al., 2008] Eckert, M. A., Kamdar, N. V., Chang, C. E., Beckmann, C. F., Greicius, M. D., and Menon, V. (2008). A cross-modal system linking primary auditory and visual cortices: Evidence from intrinsic fMRI connectivity analysis. *Human Brain Mapping*, 29(7):848–857.

[Eger et al., 2013] Eger, E., Moretti, L., Dehaene, S., and Sirigu, A. (2013). Decoding the representation of learned social roles in the human brain. *Cortex*, 49(9):2484–2493.

[Eisenberger, 2003] Eisenberger, N. I. (2003). Does Rejection Hurt? An fMRI Study of Social Exclusion. *Science*, 302(5643):290–292.

[Emberson et al., 2011] Emberson, L. L., Conway, C. M., and Christiansen, M. H. (2011). Timing is everything: Changes in presentation rate have opposite effects on auditory and visual implicit statistical learning. *Quarterly Journal of Experimental Psychology*, 64(5):1021–1040.

[Epstein and Kanwisher, 1998] Epstein, R. and Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, 392(6676):598–601.

[Fair et al., 2007] Fair, D. A., Dosenbach, N. U. F., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., and Schlaggar, B. L. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences*, 104(33):13507–13512.

[Fan et al., 2013] Fan, T., Wu, X., Yao, L., and Dong, J. (2013). Abnormal baseline brain activity in suicidal and non-suicidal patients with major depressive disorder. *Neuroscience Letters*, 534(1):35–40.

[Faraone et al., 2005] Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., and Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder.

[Fazio et al., 2009] Fazio, P., Cantagallo, A., Craighero, L., D'ausilio, A., Roy, A. C., Pozzo, T., Calzolari, F., Granieri, E., and Fadiga, L. (2009). Encoding of human action in Broca's area. *Brain*, 132(7):1980–1988.

[Fernandes et al., 2010] Fernandes, T., Kolinsky, R., and Ventura, P. (2010). The impact of attention load on the use of statistical information and coarticulation as speech segmentation cues. *Attention, Perception, & Psychophysics*, 72(6):1522–1532.

[Fiser and Aslin, 2001] Fiser, J. and Aslin, R. N. (2001). Unsupervised Statistical Learning of Higher-Order Spatial Structures from Visual Scenes. *Psychological Science*, 12(6):499–504.

[Fisher, 1995] Fisher, N. I. (1995). *Statistical analysis of circular data*. Cambridge University Press.

[Fjell et al., 2007] Fjell, A. M., Walhovd, K. B., Fischl, B., and Reinvang, I. (2007). Cognitive function, P3a/P3b brain potentials, and cortical thickness in aging. *Human Brain Mapping*, 28(11):1098–1116.

[Foster et al., 2015] Foster, B. L., Rangarajan, V., Shirer, W. R., and Parvizi, J. (2015). Intrinsic and task-dependent coupling of neuronal population activity in human parietal cortex. *Neuron*, 86(2):578–590.

[Fox and Raichle, 2007] Fox, M. D. and Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, 8(9):700–711.

[Fox et al., 2005] Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27):9673–8.

[Fox et al., 2013] Fox, M. D., Zhang, D., Snyder, A. Z., and Raichle, M. E. (2013). The Global Signal and Observed Anticorrelated Resting State Brain Networks The Global Signal and Observed Anticorrelated Resting State Brain Networks. *Journal of neurophysiology*, 101(April 2009):3270–3283.

[French et al., 2011] French, R. M., Addyman, C., and Mareschal, D. (2011). TRACX: A recognition-based connectionist framework for sequence segmentation and chunk extraction. *Psychological Review*, 118(4):614–636.

[French and Cottrell, 2014] French, R. M. and Cottrell, G. W. (2014). TRACX 2.0 : A memory-based, biologically-plausible model of sequence segmentation and chunk extraction. In *Proceedings of the 36th Annual Conference of the Cognitive Science Society*, volume 36, pages 2216–2221.

[Friederici et al., 2009] Friederici, A. D., Makuuchi, M., and Bahlmann, J. (2009). The role of the posterior superior temporal cortex in sentence comprehension. *NeuroReport*, 20(6):563–568.

[Friston, 1998] Friston, K. J. (1998). The disconnection hypothesis. In *Schizophrenia Research*, volume 30, pages 115–125.

[Friston, 2011] Friston, K. J. (2011). Functional and effective connectivity: a review. *Brain Connectivity*, 1(1):13–36.

[Frost et al., 2015] Frost, R., Armstrong, B. C., Siegelman, N., and Christiansen, M. H. (2015). Domain generality versus modality specificity: The paradox of statistical learning.

[Gebhart et al., 2009] Gebhart, A. L., Newport, E. L., and Aslin, R. N. (2009). Statistical learning of adjacent and nonadjacent dependencies among nonlinguistic sounds. *Psychonomic Bulletin & Review*, 16(3):486–490.

[Gilson et al., 2017] Gilson, M., Deco, G., Friston, K., Hagmann, P., Mantini, D., Betti, V., Romani, L., and Corbetta, M. (2017). Effective connectivity inferred from fMRI transition dynamics during movie viewing points to a balanced reconfiguration of cortical interactions. pages 122–140.

[Golestani and Zatorre, 2004] Golestani, N. and Zatorre, R. J. (2004). Learning new sounds of speech: Reallocation of neural substrates. *NeuroImage*, 21(2):494–506.

[Gordon et al., 2014] Gordon, E. M., Breeden, A. L., Bean, S. E., and Vaidya, C. J. (2014). Working memory-related changes in functional connectivity persist beyond task disengagement. *Human Brain Mapping*, 35(3):1004–1017.

[Granger, 1969] Granger, C. W. J. (1969). Investigating Causal Relations by Econometric Models and Cross-spectral Methods. *Econometrica*, 37(3):424–438.

[Greicius, 2008] Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology*, 24(4):424–430.

[Greicius et al., 2007] Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L., and Schatzberg, A. F. (2007). Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*, 62(5):429–437.

[Grèzes and Decety, 2002] Grèzes, J. and Decety, J. (2002). Does visual perception of object afford action? Evidence from a neuroimaging study. *Neuropsychologia*, 40(2):212–222.

[Grill-Spector et al., 2004] Grill-Spector, K., Knouf, N., and Kanwisher, N. (2004). The fusiform face area subserves face perception, not generic within-category identification. *Nature Neuroscience*, 7(5):555–562.

[Guidotti et al., 2015] Guidotti, R., Del Gratta, C., Baldassarre, A., Romani, G. L., and Corbetta, M. (2015). Visual Learning Induces Changes in Resting-State fMRI Multivariate Pattern of Information. *Journal of Neuroscience*, 35(27):9786–9798.

[Gusnard and Raichle, 2001] Gusnard, D. A. and Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, 2(10):685–694.

[Habas et al., 2009] Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., and Greicius, M. D. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. *Journal of Neuroscience*, 29(26):8586–8594.

[Hagmann et al., 2008] Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., and Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS biology*, 6(7):e159.

[Hahn et al., 2007] Hahn, B., Ross, T. J., and Stein, E. A. (2007). Cingulate activation increases dynamically with response speed under stimulus unpredictability. *Cerebral Cortex*, 17(7):1664–1671.

[Hampson et al., 2006] Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., and Constable, R. T. (2006). Brain Connectivity Related to Working Memory Performance. *Journal of Neuroscience*, 26(51):13338–13343.

[Han et al., 2015] Han, K., Chapman, S. B., and Krawczyk, D. C. (2015). Altered amygdala connectivity in individuals with chronic traumatic brain injury and comorbid depressive symptoms. *Frontiers in Neurology*, 6(NOV):231.

[Hassin et al., 2009] Hassin, R. R., Bargh, J. A., Engell, A. D., and McCulloch, K. C. (2009). Implicit working memory. *Consciousness and Cognition*, 18(3):665–678.

[Hattingh et al., 2013] Hattingh, C. J., Ipser, J., Tromp, S. A., Syal, S., Lochner, C., Brooks, S. J., and Stein, D. J. (2013). Functional magnetic resonance imaging during emotion recognition in social anxiety disorder: an activation likelihood meta-analysis. *Frontiers in Human Neuroscience*, 6:347.

[Haupt et al., 2009] Haupt, S., Axmacher, N., Cohen, M. X., Elger, C. E., and Fell, J. (2009). Activation of the caudal anterior cingulate cortex due to task-related interference in an auditory stroop paradigm. *Human Brain Mapping*, 30(9):3043–3056.

[Haxby et al., 2000] Haxby, J. V., Hoffman, E. A., and Gobbini, M. I. (2000). The distributed human neural system for face perception.

[He et al., 2009] He, Y., Wang, J., Wang, L., Chen, Z. J., Yan, C., Yang, H., Tang, H., Zhu, C., Gong, Q., Zang, Y., and Evans, A. C. (2009). Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PLoS ONE*, 4(4):e5226.

[Heine et al., 2012] Heine, L., Soddu, A., Gómez, F., Vanhaudenhuyse, A., Tshibanda, L., Thonnard, M., Charland-Verville, V., Kirsch, M., Laureys, S., and Demertzi, A. (2012). Resting state networks and consciousness Alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness states. *Frontiers in Psychology*, 3(AUG):295.

[Henseler et al., 2014] Henseler, I., Regenbrecht, F., and Obrig, H. (2014). Lesion correlates of patholinguistic profiles in chronic aphasia: Comparisons of syndrome-, modality-and symptom-level assessment. *Brain*, 137(3):918–930.

[Hlinka et al., 2011] Hlinka, J., Paluš, M., Vejmelka, M., Mantini, D., and Corbetta, M. (2011). Functional connectivity in resting-state fMRI: Is linear correlation sufficient? *NeuroImage*, 54(3):2218–2225.

[Hou et al., 2012] Hou, J., Wu, W., Lin, Y., Wang, J., Zhou, D., Guo, J., Gu, S., He, M., Ahmed, S., Hu, J., Qu, W., and Li, H. (2012). Localization of cerebral functional deficits in patients with obsessive-compulsive disorder: A resting-state fMRI study. *Journal of Affective Disorders*, 138(3):313–321.

[Hull et al., 2017] Hull, J. V., Jacokes, Z. J., Torgerson, C. M., Irimia, A., Van Horn, J. D., Aylward, E., Bernier, R., Bookheimer, S., Dapretto, M., Gaab, N., Geschwind, D., Jack, A., Nelson, C., Pelphrey, K., State, M., Ventola, P., and Webb, S. J. (2017). Resting-state functional connectivity in autism spectrum disorders: A review.

[Humphries and Gurney, 2008] Humphries, M. D. and Gurney, K. (2008). Network 'small-world-ness': A quantitative method for determining canonical network equivalence. *PLoS ONE*, 3(4):e0002051.

[Iacobucci et al., 2015] Iacobucci, D., Posavac, S. S., Kardes, F. R., Schneider, M. J., and Popovich, D. L. (2015). The median split: Robust, refined, and revived. *Journal of Consumer Psychology*, 25(4):690–704.

[Jack et al., 2013] Jack, A. I., Dawson, A. J., Begany, K. L., Leckie, R. L., Barry, K. P., Ciccia, A. H., and Snyder, A. Z. (2013). fMRI reveals reciprocal inhibition between social and physical cognitive domains. *NeuroImage*, 66:385–401.

[Jafri et al., 2008] Jafri, M. J., Pearlson, G. D., Stevens, M., and Calhoun, V. D. (2008). A method for functional network connectivity among spatially independent resting-state components in schizophrenia. *NeuroImage*, 39(4):1666–1681.

[James, 1890] James, W. (1890). *The principles of psychology.* Dover Publications.

[Johnson and Jusczyk, 2003] Johnson, E. K. and Jusczyk, P. W. (2003). Exploring possible effects of language-specific knowledge on infants' segmentation of an artificial language.

[Jolles et al., 2013] Jolles, D. D., Van Buchem, M. A., Crone, E. A., and Rombouts, S. A. R. B. (2013). Functional brain connectivity at rest changes after working memory training. *Human Brain Mapping*, 34(2):396–406.

[Jung et al., 2014] Jung, M., Kosaka, H., Saito, D. N., Ishitobi, M., Morita, T., Inohara, K., Asano, M., Arai, S., Munesue, T., Tomoda, A., Wada, Y., Sadato, N., Okazawa, H., and Iidaka, T. (2014). Default mode network in young male adults with autism spectrum disorder: relationship with autism spectrum traits. *Molecular Autism*, 5(1):35.

[Karafin et al., 2004] Karafin, M. S., Tranel, D., and Adolphs, R. (2004). Dominance attributions following damage to the ventromedial prefrontal cortex. *Journal of cognitive neuroscience*, 16(10):1796–1804.

[Karpicke and Pisoni, 2004] Karpicke, J. D. and Pisoni, D. B. (2004). Using immediate memory span to measure implicit learning. *Memory and Cognition*, 32(6):956–964.

[Kastrati et al., 2011] Kastrati, A., Neumann, F.-J., Schulz, S., Massberg, S., Byrne, R. A., Ferenc, M., Laugwitz, K.-L., Pache, J., Ott, I., Hausleiter, J., Seyfarth, M., Gick, M., Antoniucci, D., Schömig, A., Berger, P. B., Mehilli, J., and Investigators, I.-R. . T. (2011). Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *New England Journal of Medicine*, 365(21):1980–1989.

[Katsuki and Constantinidis, 2014] Katsuki, F. and Constantinidis, C. (2014). Bottom-Up and Top-Down Attention. *The Neuroscientist*, 20(5):509–521.

[Kennedy et al., 2006] Kennedy, D. P., Redcay, E., and Courchesne, E. (2006). Failing to deactivate: resting functional abnormalities in autism. *Proceedings of the National Academy of Sciences of the United States of America*, 103(21):8275–8280.

[Kim et al., 2009] Kim, R., Seitz, A., Feenstra, H., and Shams, L. (2009). Testing assumptions of statistical learning: Is it long-term and implicit? *Neuroscience Letters*, 461(2):145–149.

[Kim et al., 2013] Kim, S., Chen, Z., Zhang, Z., Simons-Morton, B. G., and Albert, P. S. (2013). Bayesian Hierarchical Poisson Regression Models: An Application to a Driving Study With Kinematic Events. *Journal of the American Statistical Association*, 108502(502):494–503.

[Kim et al., 1994] Kim, S. G., UÄurbil, K., and Strick, P. L. (1994). Activation of a cerebellar output nucleus during cognitive processing. *Science (New York, N.Y.)*, 265(5174):949–951.

[Kitzbichler et al., 2009] Kitzbichler, M. G., Smith, M. L., Christensen, S. R., and Bullmore, E. (2009). Broadband criticality of human brain network synchronization. *PLoS Computational Biology*, 5(3):e1000314.

[Konrad and Eickhoff, 2010] Konrad, K. and Eickhoff, S. B. (2010). Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder.

[Koyama et al., 2011] Koyama, M. S., Di Martino, A., Zuo, X.-N., Kelly, C., Mennes, M., Jutagir, D. R., Castellanos, F. X., and Milham, M. P. (2011). Resting-State Functional Connectivity Indexes Reading Competence in Children and Adults. *Journal of Neuroscience*, 31(23):8617–8624.

[Kraskov et al., 2004] Kraskov, A., Stögbauer, H., and Grassberger, P. (2004). Estimating mutual information. *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics*, 69(6 2):066138.

[Krawczyk, 2002] Krawczyk, D. C. (2002). Contributions of the prefrontal cortex to the neural basis of human decision making.

[Kumaran et al., 2012] Kumaran, D., Melo, H. L., and Duzel, E. (2012). The Emergence and Representation of Knowledge about Social and Nonsocial Hierarchies. *Neuron*, 76(3):653–666.

[Laird et al., 2011] Laird, A. R., Fox, P. M., Eickhoff, S. B., Turner, J. A., Ray, K. L., McKay, D. R., Glahn, D. C., Beckmann, C. F., Smith, S. M., and Fox, P. T. (2011). Behavioral interpretations of intrinsic connectivity networks. *Journal of cognitive neuroscience*, 23(12):4022–37.

[Lane et al., 1997] Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., and Schwartz, G. E. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia*, 35(11):1437–1444.

[Laureys et al., 2004] Laureys, S., Owen, A. M., and Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders.

[Leech et al., 2012] Leech, R., Braga, R., and Sharp, D. J. (2012). Echoes of the Brain within the Posterior Cingulate Cortex. *Journal of Neuroscience*, 32(1):215–222.

[Leech and Sharp, 2014] Leech, R. and Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease.

[Lewis et al., 2009] Lewis, C. M., Baldassarre, A., Committeri, G., Romani, G. L., and Corbetta, M. (2009). Learning sculpts the spontaneous activity of the resting human brain. *Proceedings of the National Academy of Sciences*, 106(41):17558–17563.

[Li et al., 2014a] Li, F., He, N., Li, Y., Chen, L., Huang, X., Lui, S., Guo, L., Kemp, G. J., and Gong, Q. (2014a). Intrinsic Brain Abnormalities in Attention Deficit Hyperactivity Disorder: A Resting-State Functional MR Imaging Study. *Radiology*, 272(2):514–523.

[Li et al., 2012] Li, M., Chen, Z., and Li, T. (2012). Small-world brain networks in schizophrenia. *Shanghai archives of psychiatry*, 24(6):322–7.

[Li et al., 2002] Li, S.-J., Li, Z., Wu, G., Zhang, M.-J., Franczak, M., and Antuono, P. G. (2002). Alzheimer Disease: evaluation of a functional MR imaging index as a marker. *Radiology*, 225(1):253–259.

[Li et al., 2014b] Li, W., Li, Y., Zhu, W., and Chen, X. (2014b). Changes in brain functional network connectivity after stroke. *Neural Regeneration Research*, 9(1):51–60.

[Lieberman and Cunningham, 2009] Lieberman, M. D. and Cunningham, W. A. (2009). Type I and Type II error concerns in fMRI research: Re-balancing the scale. *Social Cognitive and Affective Neuroscience*, 4(4):423–428.

[Linden, 2007] Linden, D. E. (2007). The Working Memory Networks of the Human Brain. *The Neuroscientist*, 13(3):257–267.

[Lindner et al., 2011] Lindner, M., Vicente, R., Priesemann, V., and Wibral, M. (2011). TRENTOOL: A Matlab open source toolbox to analyse information flow in time series data with transfer entropy. *BMC Neuroscience*, 12(1):119.

[Lindquist et al., 2012] Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., and Barrett, L. F. (2012). The brain basis of emotion: A meta-analytic review. *Behavioral and Brain Sciences*, 35(03):121–2002.

[Littow et al., 2015] Littow, H., Huossa, V., Karjalainen, S., Jääskeläinen, E., Haapea, M., Miettunen, J., Tervonen, O., Isohanni, M., Nikkinen, J., Veijola, J., Murray, G., and Kiviniemi, V. J. (2015). Aberrant functional connectivity in the default mode and central executive networks in subjects with schizophrenia - a whole-brain resting-state ICA study. *Frontiers in Psychiatry*, 6(FEB):26.

[Liu et al., 2006] Liu, H., Liu, Z., Liang, M., Hao, Y., Tan, L., Kuang, F., Yi, Y., Xu, L., and Jiang, T. (2006). Decreased regional homogeneity in schizophrenia: a resting state functional magnetic resonance imaging study. *Neuroreport*, 17(1):19–22.

[Liu et al., 2014] Liu, J., Ren, L., Womer, F. Y., Wang, J., Fan, G., Jiang, W., Blumberg, H. P., Tang, Y., Xu, K., and Wang, F. (2014). Alterations in amplitude of low frequency fluctuation in treatment-naïve major depressive disorder measured with resting-state fMRI. *Human Brain Mapping*, 35(10):4979–4988.

[Liu et al., 2008] Liu, Y., Wang, K., YU, C., He, Y., Zhou, Y., Liang, M., Wang, L., and Jiang, T. (2008). Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: A review of resting-state fMRI studies. *Neuropsychologia*, 46(6):1648–1656.

[Lohmann et al., 2010] Lohmann, G., Margulies, D. S., Horstmann, A., Pleger, B., Lepsien, J., Goldhahn, D., Schloegl, H., Stumvoll, M., Villringer, A., and Turner, R. (2010). Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain. *PLoS ONE*, 5(4):e10232.

[Long et al., 2008] Long, X.-Y., Zuo, X.-N., Kiviniemi, V. J., Yang, Y., Zou, Q.-H., Zhu, C.-Z., Jiang, T.-Z., Yang, H., Gong, Q.-Y., Wang, L., Li, K.-C., Xie, S., and Zang, Y.-F. (2008). Default mode network as revealed with multiple methods for resting-state functional MRI analysis. *Journal of neuroscience methods*, 171(2):349–55.

[Lopez-Barroso et al., 2013] Lopez-Barroso, D., Catani, M., Ripolles, P., Dell'Acqua, F., Rodriguez-Fornells, A., and de Diego-Balaguer, R. (2013). Word learning is mediated by the left arcuate fasciculus. *Proceedings of the National Academy of Sciences*, 110(32):13168–13173.

[Lowe et al., 1998] Lowe, M., Mock, B., and Sorenson, J. (1998). Functional Connectivity in Single and Multislice Echoplanar Imaging Using Resting-State Fluctuations. *NeuroImage*, 7(2):119–132.

[MacCallum et al., 2002] MacCallum, R. C., Zhang, S., Preacher, K. J., and Rucker, D. D. (2002). On the practice of dichotomization of quantitative variables. *Psychological methods*, 7(1):19–40.

[Mantini et al., 2012] Mantini, D., Hasson, U., Betti, V., Perrucci, M. G., Romani, G. L., Corbetta, M., Orban, G. A., and Vanduffel, W. (2012). Interspecies activity correlations reveal functional correspondence between monkey and human brain areas. *Nature methods*, 9(3):277–82.

[Mar, 2011] Mar, R. A. (2011). The neural bases of social cognition and story comprehension. *Annual review of psychology*, 62(1):103–134.

[Margulies et al., 2007] Margulies, D., Kelly, A., Uddin, L., Biswal, B., Castellanos, F., and Milham, M. (2007). Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage*, 37(2):579–588.

[Mars et al., 2012] Mars, R. B., Neubert, F.-X., Noonan, M. P., Sallet, J., Toni, I., and Rushworth, M. F. S. (2012). On the relationship between the âdefault mode networkâ and the âsocial brainâ. *Frontiers in Human Neuroscience*, 6(June):1–9.

[Marsh et al., 2009] Marsh, A. A., Blair, K. S., Jones, M. M., Soliman, N., and Blair, R. J. R. (2009). Dominance and Submission: The Ventrolateral Prefrontal Cortex and Responses to Status Cues. *Journal of Cognitive Neuroscience*, 21(4):713–724.

[Martínez et al., 2013] Martínez, K., Solana, A. B., Burgaleta, M., Hernández-Tamames, J. A., Álvarez-Linera, J., Román, F. J., Alfayate, E., Privado, J., Escorial, S., Quiroga, M. A., Karama, S., Bellec, P., and Colom, R. (2013). Changes in resting-state functionally connected parietofrontal networks after videogame practice. *Human Brain Mapping*, 34(12):3143–3157.

[Mayr, 1996] Mayr, U. (1996). Spatial attention and implicit sequence learning: evidence for independent learning of spatial and nonspatial sequences. *Journal of Experimental Psychology*, 22(2):350–364.

[McCarthy et al., 2013] McCarthy, M. S., Jensvold, M. L. A., and Fouts, D. H. (2013). Use of gesture sequences in captive chimpanzee (Pan troglodytes) play. *Animal Cognition*, 16(3):471–481.

[McClelland et al., 2015] McClelland, G. H., Lynch, J. G., Irwin, J. R., Spiller, S. A., and Fitzsimons, G. J. (2015). Median splits, Type II errors, and false-positive consumer psychology: Don't fight the power. *Journal of Consumer Psychology*, 25(4):679–689.

[McNealy et al., 2006] McNealy, K., Mazziotta, J. C., and Dapretto, M. (2006). Cracking the Language Code: Neural Mechanisms Underlying Speech Parsing. *Journal of Neuroscience*, 26(29):7629–7639.

[McNealy et al., 2010] McNealy, K., Mazziotta, J. C., and Dapretto, M. (2010). The neural basis of speech parsing in children and adults. *Developmental Science*, 13(2):385–406.

[Mehta et al., 2008] Mehta, P. H., Jones, A. C., and Josephs, R. A. (2008). The social endocrinology of dominance: Basal testosterone predicts cortisol changes and behavior following victory and defeat. *Journal of Personality and Social Psychology*, 94(6):1078–1093.

[Mende-siedlecki et al., 2013] Mende-siedlecki, P., Said, C. P., and Todorov, A. (2013). The social evaluation of faces: A meta-analysis of functional neuroimaging studies. *Social Cognitive and Affective Neuroscience*, 8(3):285–299.

[Mennes et al., 2012] Mennes, M., Potler, N. V., Kelly, C., Di Martino, A., Castellanos, F. X., and Milham, M. P. (2012). Resting state functional connectivity correlates of inhibitory control in children with attention-deficit/hyperactivity disorder. *Frontiers in Psychiatry*, 2(JAN):83.

[Menon and Uddin, 2010] Menon, V. and Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function.

[Mingoia et al., 2012] Mingoia, G., Wagner, G., Langbein, K., Maitra, R., Smesny, S., Dietzek, M., Burmeister, H. P., Reichenbach, J. R., Schlösser, R. G. M., Gaser, C., Sauer, H., and Nenadic, I. (2012). Default mode network activity in schizophrenia studied at resting state using probabilistic ICA. *Schizophrenia Research*, 138(2-3):143–149.

[Misyak and Christiansen, 2012] Misyak, J. B. and Christiansen, M. H. (2012). Statistical Learning and Language: An Individual Differences Study. *Language Learning*, 62(1):302–331.

[Miyashita, 1988] Miyashita, Y. (1988). Neuronal correlate of visual associative long-term memory in the primate temporal cortex. *Nature*, 335(6193):817–820.

[Mohammadi et al., 2009] Mohammadi, B., Kollewe, K., Samii, A., Krampfl, K., Dengler, R., and Münte, T. F. (2009). Changes of resting state brain networks in amyotrophic lateral sclerosis. *Experimental Neurology*, 217(1):147–153.

[Mulders et al., 2015] Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., and Tendolkar, I. (2015). Resting-state functional connectivity in major depressive disorder: A review.

[Murdaugh et al., 2012] Murdaugh, D. L., Shinkareva, S. V., Deshpande, H. R., Wang, J., Pennick, M. R., and Kana, R. K. (2012). Differential Deactivation during Mentalizing and Classification of Autism Based on Default Mode Network Connectivity. *PLoS ONE*, 7(11):e50064.

[Murphy et al., 2009] Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., and Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *NeuroImage*, 44(3):893–905.

[Murphy and Fox, 2017] Murphy, K. and Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *NeuroImage*, 154:169–173.

[Muscatell et al., 2012] Muscatell, K. A., Morelli, S. A., Falk, E. B., Way, B. M., Pfeifer, J. H., Galinsky, A. D., Lieberman, M. D., Dapretto, M., and Eisenberger, N. I. (2012). Social status modulates neural activity in the mentalizing network. *NeuroImage*, 60(3):1771–1777.

[Nachev et al., 2008] Nachev, P., Kennard, C., and Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature reviews. Neuroscience*, 9(11):856–869.

[Nakamura et al., 2009] Nakamura, T., Hillary, F. G., and Biswal, B. B. (2009). Resting network plasticity following brain injury. *PLoS ONE*, 4(12):e8220.

[Nee et al., 2013] Nee, D. E., Brown, J. W., Askren, M. K., Berman, M. G., Demiralp, E., Krawitz, A., and Jonides, J. (2013). A meta-Analysis of executive components of working memory. *Cerebral Cortex*, 23(2):264–282.

[Neger et al., 2014] Neger, T. M., Rietveld, T., and Janse, E. (2014). Relationship between perceptual learning in speech and statistical learning in younger and older adults. *Frontiers in Human Neuroscience*, 8:628.

[Nichols and Holmes, 2002] Nichols, T. E. and Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, 15(1):1–25.

[Norman et al., 2006] Norman, K. A., Polyn, S. M., Detre, G. J., and Haxby, J. V. (2006). Beyond mind-reading: multi-voxel pattern analysis of fMRI data.

[Obleser and Kotz, 2010] Obleser, J. and Kotz, S. A. (2010). Expectancy constraints in degraded speech modulate the language comprehension network. *Cerebral Cortex*, 20(3):633–640.

[Olde Dubbelink et al., 2014] Olde Dubbelink, K. T., Hillebrand, A., Stoffers, D., Deijen, J. B., Twisk, J. W., Stam, C. J., and Berendse, H. W. (2014). Disrupted brain network topology in Parkinson's disease: A longitudinal magnetoencephalography study. *Brain*, 137(1):197–207.

[Oosterhof and Todorov, 2008] Oosterhof, N. N. and Todorov, A. (2008). The functional basis of face evaluation. *Proceedings of the National Academy of Sciences*, 105(32):11087–11092.

[O'Reilly et al., 2010] O'Reilly, J. X., Beckmann, C. F., Tomassini, V., Ramnani, N., and Johansen-Berg, H. (2010). Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cerebral Cortex*, 20(4):953–965.

[Pacton et al., 2015] Pacton, S., Sobaco, A., and Perruchet, P. (2015). Is an attention-based associative account of adjacent and nonadjacent dependency learning valid? *Acta Psychologica*, 157(1):195–199.

[Pajula et al., 2012] Pajula, J., Kauppi, J. P., and Tohka, J. (2012). Inter-subject correlation in fMRI: Method validation against stimulus-model based analysis. *PLoS ONE*, 7(8).

[Pajula and Tohka, 2016] Pajula, J. and Tohka, J. (2016). How Many Is Enough? Effect of Sample Size in Inter-Subject Correlation Analysis of fMRI. *Computational Intelligence and Neuroscience*, 2016.

[Palmer and Mattys, 2016] Palmer, S. D. and Mattys, S. L. (2016). Speech segmentation by statistical learning is supported by domain-general processes within working memory. *Quarterly Journal of Experimental Psychology*, 69(12):2390–2401.

[Palva et al., 2010] Palva, J. M., Monto, S., Kulashekhar, S., and Palva, S. (2010). Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proceedings of the National Academy of Sciences of the United States of America*, 107(16):7580–5.

[Parker et al., 2005] Parker, G. J. M., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A. M., Ciccarelli, O., and Lambon Ralph, M. A. (2005). Lateralization of ventral and dorsal auditory-language pathways in the human brain. *NeuroImage*, 24(3):656–666.

[Paulus and Frank, 2003] Paulus, M. P. and Frank, L. R. (2003). Ventromedial prefrontal cortex activation is critical for preference judgments. *NeuroReport*, 14(10):1311–1315.

[Pelucchi et al., 2009] Pelucchi, B., Hay, J. F., and Saffran, J. R. (2009). Statistical Learning in a Natural Language by 8-Month-Old Infants. *Child Development*, 80(3):674–685.

[Perruchet and Vinter, 1998] Perruchet, P. and Vinter, A. (1998). PARSER: A Model for Word Segmentation. *Journal of Memory and Language*, 39(2):246–263.

[Petersen et al., 1998] Petersen, S. E., van Mier, H., Fiez, J. A., and Raichle, M. E. (1998). The effects of practice on the functional anatomy of task performance. *Proceedings of the National Academy of Sciences*, 95(3):853–860.

[Plaisted Grant and Davis, 2009] Plaisted Grant, K. and Davis, G. (2009). Perception and apperception in autism: rejecting the inverse assumption. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*, 364(1522):1393–1398.

[Ponce-Alvarez et al., 2015] Ponce-Alvarez, A., Deco, G., Hagmann, P., Romani, G. L., Mantini, D., and Corbetta, M. (2015). Resting-State Temporal Synchronization Networks Emerge from Connectivity Topology and Heterogeneity. *PLoS Computational Biology*, 11(2).

[Prasad et al., 2005] Prasad, K. M. R., Sahni, S. D., Rohm, B. R., and Keshavan, M. S. (2005). Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. *Psychiatry Research - Neuroimaging*, 140(2):147–155.

[Pugh et al., 1996] Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Byrd, D., Skudlarski, P., Shankweiler, D. P., Katz, L., Constable, R., Fletcher, J., Lacadie, C., Marchione, K., and Gore, J. C. (1996). Auditory Selective Attention: An fMRI Investigation. *NeuroImage*, 4(3):159–173.

[Qi et al., 2010] Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L., and Li, K. (2010). Impairment and compensation coexist in amnestic MCI default mode network. *NeuroImage*, 50(1):48–55.

[Raettig et al., 2010] Raettig, T., Frisch, S., Friederici, A. D., and Kotz, S. A. (2010). Neural correlates of morphosyntactic and verb-argument structure processing: An EfMRI study. *Cortex*, 46(5):613–620.

[Raichle, 2015] Raichle, M. E. (2015). The Brain's Default Mode Network. *Annual Review of Neuroscience*, 38(1):433–447.

[Raichle et al., 2001] Raichle, M. E., MacLeod, a. M., Snyder, a. Z., Powers, W. J., Gusnard, D. a., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. USA*, 98(2):676–82.

[Raichle and Mintun, 2006] Raichle, M. E. and Mintun, M. A. (2006). Brain Work and Brain Imaging. *Annual Review of Neuroscience*, 29(1):449–476.

[Reilhac et al., 2013] Reilhac, C., Peyrin, C., Démonet, J.-F., and Valdois, S. (2013). Role of the superior parietal lobules in letter-identity processing within strings: fMRI evidence from skilled and dyslexicreaders. *Neuropsychologia*, 51(4):601–612.

[Roberts and Hall, 2008] Roberts, K. L. and Hall, D. A. (2008). Examining a Supramodal Network for Conflict Processing: A Systematic Review and Novel Functional Magnetic Resonance Imaging Data for Related Visual and Auditory Stroop Tasks. *Journal of Cognitive Neuroscience*, 20(6):1063–1078.

[Roy et al., 2009] Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Gotimer, K., Biswal, B. B., Castellanos, F. X., and Milham, M. P. (2009). Functional connectivity of the human amygdala using resting state fMRI. *NeuroImage*, 45(2):614–626.

[Rubinov et al., 2009] Rubinov, M., Knock, S. A., Stam, C. J., Micheloyannis, S., Harris, A. W., Williams, L. M., and Breakspear, M. (2009). Small-world properties of nonlinear brain activity in schizophrenia. *Human Brain Mapping*, 30(2):403–416.

[Rucker et al., 2015] Rucker, D. D., McShane, B. B., and Preacher, K. J. (2015). A researcher's guide to regression, discretization, and median splits of continuous variables. *Journal of Consumer Psychology*, 25(4):666–678.

[Rushworth et al., 2013] Rushworth, M. F. S., Mars, R. B., and Sallet, J. (2013). Are there specialized circuits for social cognition and are they unique to humans?

[Saffran et al., 1996] Saffran, J. R., Aslin, R. N., and Newport, E. L. (1996). Statistical Learning by 8-Month-Old Infants. *Science*, 274(5294):1926–1928.

[Salvador et al., 2005] Salvador, R., Suckling, J., Coleman, M. R., Pickard, J. D., Menon, D., and Bullmore, E. (2005). Neurophysiological architecture of functional magnetic resonance images of human brain. *Cerebral Cortex*, 15(9):1332–2342.

[Sämann et al., 2011] Sämann, P. G., Wehrle, R., Hoehn, D., Spoormaker, V. I., Peters, H., Tully, C., Holsboer, F., and Czisch, M. (2011). Development of the brain's default mode network from wakefulness to slow wave sleep. *Cerebral Cortex*, 21(9):2082–2093.

[Santamaría-García et al., 2015] Santamaría-García, H., Burgaleta, M., and Sebastian-Galles, N. (2015). Neuroanatomical Markers of Social Hierarchy Recognition in Humans: A Combined ERP/MRI Study. *Journal of Neuroscience*, 35(30):10843–10850.

[Santamaría-García et al., 2013] Santamaría-García, H., Pannunzi, M., Ayneto, A., Deco, G., and Sebastián-Gallés, N. (2013). 'If you are good, i get better': The role of social hierarchy in perceptual decision-making. *Social Cognitive and Affective Neuroscience*, 9(10):1489–1497.

[Santamaría-García et al., 2017] Santamaría-García, H., Soriano-Mas, C., Burgaleta, M., Ayneto, A., Alonso, P., Menchón, J. M., Cardoner, N., and Sebastián-Gallés, N. (2017). Social context modulates cognitive markers in Obsessive-Compulsive Disorder.

[Santi and Grodzinsky, 2007] Santi, A. and Grodzinsky, Y. (2007). Working memory and syntax interact in Broca's area. *NeuroImage*, 37(1):8–17.

[Santolin et al., 2016] Santolin, C., Rosa-Salva, O., Vallortigara, G., and Regolin, L. (2016). Unsupervised statistical learning in newly hatched chicks.

[Sapolsky, 2004] Sapolsky, R. M. (2004). Social status and health in humans and other animals. *Annual Review of Anthropology*, 33(2004):393–418.

[Sapolsky, 2005] Sapolsky, R. M. (2005). The Influence of Social Hierarchy on Primate Health. *Science*, 308(5722):648–652.

[Schilbach et al., 2008] Schilbach, L., Eickhoff, S. B., Rotarska-Jagiela, A., Fink, G. R., and Vogeley, K. (2008). Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. *Consciousness and Cognition*, 17(2):457–467.

[Schmithorst et al., 2007] Schmithorst, V. J., Holland, S. K., and Plante, E. (2007). Object identification and lexical/semantic access in children: A functional magnetic resonance imaging study of word-picture matching. *Human Brain Mapping*, 28(10):1060–1074.

[Seeley et al., 2007] Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., and Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neuroscience*, 27(9):2349–2356.

[Shi and Malik, 2000] Shi, J. and Malik, J. (2000). Normalized cuts and image segmentation. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 22(8):888–905.

[Shomstein and Yantis, 2006] Shomstein, S. and Yantis, S. (2006). Parietal Cortex Mediates Voluntary Control of Spatial and Nonspatial Auditory Attention. *Brain*, 26(2):435– 439.

[Shulman et al., 2004] Shulman, R. G., Rothman, D. L., Behar, K. L., and Hyder, F. (2004). Energetic basis of brain activity: Implications for neuroimaging.

[Simons et al., 2014] Simons, L. E., Elman, I., and Borsook, D. (2014). Psychological processing in chronic pain: A neural systems approach.

[Singh et al., 2011] Singh, K. P., Basant, N., and Gupta, S. (2011). Support vector machines in water quality management. *Analytica Chimica Acta*, 703(2):152–162.

[Smith et al., 2009] Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., and Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*, 106(31):13040–13045.

[Söderqvist et al., 2012] Söderqvist, S., Nutley, S. B., Peyrard-Janvid, M., Matsson, H., Humphreys, K., Kere, J., and Klingberg, T. (2012). Dopamine, working memory, and training induced plasticity: Implications for developmental research. *Developmental Psychology*, 48(3):836–843.

[Sonuga-Barke and Castellanos, 2007] Sonuga-Barke, E. J. S. and Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis.

[Sorg et al., 2007] Sorg, C., Riedl, V., Muhlau, M., Calhoun, V. D., Eichele, T., Laer, L., Drzezga, A., Forstl, H., Kurz, A., Zimmer, C., and Wohlschlager, A. M. (2007). Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences*, 104(47):18760–18765.

[Spreng et al., 2016] Spreng, R. N., Stevens, W. D., Viviano, J. D., and Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. *Neurobiology of Aging*, 45:149–160.

[Stam, 2004] Stam, C. J. (2004). Functional connectivity patterns of human magnetoencephalographic recordings: A 'small-world' network? *Neuroscience Letters*, 355(1-2):25–28.

[Stanley and Adolphs, 2013] Stanley, D. A. and Adolphs, R. (2013). Toward a neural basis for social behavior.

[Stevens and Spreng, 2014] Stevens, W. D. and Spreng, R. N. (2014). Resting-state functional connectivity MRI reveals active processes central to cognition. *Wiley Interdisciplinary Reviews: Cognitive Science*, 5(2):233–245.

[Storey, 2002] Storey, J. D. (2002). A direct approach to false discovery rates. *Journal of the Royal Statistical Society. Series B: Statistical Methodology*, 64(3):479–498.

[Suckling et al., 2010] Suckling, J., Barnes, A., Job, D., Brenan, D., Lymer, K., Dazzan, P., Marques, T. R., MacKay, C., McKie, S., Williams, S. R., Williams, S. C. R., Lawrie, S., and Deakin, B. (2010). Power calculations for multicenter imaging studies controlled by the false discovery rate. *Human Brain Mapping*, 31(8):1183–1195.

[Supekar et al., 2008] Supekar, K., Menon, V., Rubin, D., Musen, M., and Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*, 4(6):e1000100.

[Swingley, 2005] Swingley, D. (2005). 11-month-olds' knowledge of how familiar words sound.

[Szczepanski et al., 2010] Szczepanski, S. M., Konen, C. S., and Kastner, S. (2010). Mechanisms of spatial attention control in frontal and parietal cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 30(1):148–60.

[Tabert et al., 2001] Tabert, M. H., Borod, J. C., Tang, C. Y., Lange, G., Wei, T. C., Johnson, R., Nusbaum, A. O., and Buchsbaum, M. S. (2001). Differential amygdala activation during emotional decision and recognition memory tasks using unpleasant words: An fMRI study. *Neuropsychologia*, 39(6):556–573.

[Thiessen et al., 2013] Thiessen, E. D., Kronstein, A. T., and Hufnagle, D. G. (2013). The extraction and integration framework: A two-process account of statistical learning. *Psychological Bulletin*, 139(4):792–814.

[Toro et al., 2005] Toro, J. M., Sinnett, S., and Soto-Faraco, S. (2005). Speech segmentation by statistical learning depends on attention. *Cognition*, 97(2):B25–B34.

[Tracey and Mantyh, 2007] Tracey, I. and Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation.

[Trautmann et al., 2009] Trautmann, S. A., Fehr, T., and Herrmann, M. (2009). Emotions in motion: Dynamic compared to static facial expressions of disgust and happiness reveal more widespread emotion-specific activations. *Brain Research*, 1284:100–115.

[Tung et al., 2013] Tung, K. C., Uh, J., Mao, D., Xu, F., Xiao, G., and Lu, H. (2013). Alterations in resting functional connectivity due to recent motor task. *NeuroImage*, 78:316–324.

[Turk et al., 2004] Turk, D. J., Banfield, J. F., Walling, B. R., Heatherton, T. F., Grafton, S. T., Handy, T. C., Gazzaniga, M. S., and Macrae, C. N. (2004). From facial cue to dinner for two: The neural substrates of personal choice. *NeuroImage*, 22(3):1281–1290.

[Turk-Browne et al., 2005] Turk-Browne, N. B., Jungé, J. A., and Scholl, B. J. (2005). The Automaticity of Visual Statistical Learning. *Journal of Experimental Psychology: General*, 134(4):552–564.

[Uddin, 2014] Uddin, L. Q. (2014). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, 16(1):55–61.

[Ullman, 2004] Ullman, M. T. (2004). Contributions of memory circuits to language: The declarative/procedural model. *Cognition*, 92(1-2):231–270.

[Ullman, 2005] Ullman, M. T. (2005). The Declarative/Procedural Model. In *Neurobiology of Language*, pages 953–968.

[Usrey et al., 1998] Usrey, W. M., Reppas, J. B., and Reid, R. C. (1998). Paired-spike interactions and synaptic efficacy of retinal inputs to the thalamus. *Nature*, 395(SEPTEMBER):384–387.

[Vahdat et al., 2011] Vahdat, S., Darainy, M., Milner, T. E., and Ostry, D. J. (2011). Functionally Specific Changes in Resting-State Sensorimotor Networks after Motor Learning. *Journal of Neuroscience*, 31(47):16907–16915.

[Valencia et al., 2009] Valencia, M., Pastor, M. A., Fernandez-Seara, M. A., Artieda, J., Martinerie, J., and Chavez, M. (2009). Complex modular structure of large-scale brain networks. *Chaos*, 19(2):023119.

[van den Heuvel et al., 2008] van den Heuvel, M., Mandl, R., and Pol, H. H. (2008). Normalized cut group clustering of resting-state fMRI data. *PLoS ONE*, 3(4):e2001.

[van den Heuvel and Hulshoff Pol, 2010] van den Heuvel, M. P. and Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity.

[Vanderwal et al., 2008] Vanderwal, T., Hunyadi, E., Grupe, D. W., Connors, C. M., and Schultz, R. T. (2008). Self, mother and abstract other: An fMRI study of reflective social processing. *NeuroImage*, 41(4):1437–1446.

[Vanhaudenhuyse et al., 2010] Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L. J. F., Bruno, M. A., Boveroux, P., Schnakers, C., Soddu, A., Perlbarg, V., Ledoux, D., Brichant, J. F., Moonen, G., Maquet, P., Greicius, M. D., Laureys, S., and Boly, M. (2010). Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain*, 133(1):161–171.

[Ventura-Campos et al., 2013] Ventura-Campos, N., Sanjuan, A., Gonzalez, J., Palomar-Garcia, M.-A., Rodriguez-Pujadas, A., Sebastian-Galles, N., Deco, G., and Avila, C. (2013). Spontaneous Brain Activity Predicts Learning Ability of Foreign Sounds. *Journal of Neuroscience*, 33(22):9295–9305.

[Veroude et al., 2010] Veroude, K., Norris, D. G., Shumskaya, E., Gullberg, M., and Indefrey, P. (2010). Functional connectivity between brain regions involved in learning words of a new language. *Brain and Language*, 113(1):21–27.

[Vicente et al., 2011] Vicente, R., Wibral, M., Lindner, M., and Pipa, G. (2011). Transfer entropy-a model-free measure of effective connectivity for the neurosciences. *Journal of Computational Neuroscience*, 30(1):45–67.

[Vincent et al., 2010] Vincent, J. L., Kahn, I., Van Essen, D. C., and Buckner, R. L. (2010). Functional connectivity of the macaque posterior parahippocampal cortex. *Journal of neurophysiology*, 103(2):793–800.

[Vogt and Laureys, 2005] Vogt, B. A. and Laureys, S. (2005). Posterior cingulate, precuneal and retrosplenial cortices: Cytology and components of the neural network correlates of consciousness.

[Wager and Smith, 2003] Wager, T. D. and Smith, E. E. (2003). Neuroimaging studies of working memory:. *Cognitive, Affective, & Behavioral Neuroscience*, 3(4):255–274.

[Walhovd et al., 2005] Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Fischl, B., Salat, D., Quinn, B. T., Makris, N., and Dale, A. M. (2005). Cortical volume and speed-of-processing are complementary in prediction of performance intelligence. *Neuropsychologia*, 43(5):704–713.

[Wang et al., 2016] Wang, C., Ong, J. L., Patanaik, A., Zhou, J., and Chee, M. W. L. (2016). Spontaneous eyelid closures link vigilance fluctuation with fMRI dynamic connectivity states. *Proceedings of the National Academy of Sciences*, 113(34):9653–9658.

[Wang et al., 2014] Wang, H. E., B??nar, C. G., Quilichini, P. P., Friston, K. J., Jirsa, V. K., and Bernard, C. (2014). A systematic framework for functional connectivity measures. *Frontiers in Neuroscience*, 8(DEC):405.

[Wang et al., 2010] Wang, L., Negreira, A., LaViolette, P., Bakkour, A., Sperling, R. A., and Dickerson, B. C. (2010). Intrinsic interhemispheric hippocampal functional connectivity predicts individual differences in memory performance ability. *Hippocampus*, 20(3):345–351.

[Wang et al., 2006] Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., Wu, T., Jiang, T., and Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. *NeuroImage*, 31(2):496–504.

[Watanabe and Yamamoto, 2015] Watanabe, N. and Yamamoto, M. (2015). Neural mechanisms of social dominance. *Frontiers in Neuroscience*, 9:154.

[Watts and Strogatz, 1999] Watts, D. J. and Strogatz, S. H. H. (1999). Collective dynamics of 'small-world' networks. *Nature*, 393(6684):440–442.

[Wei et al., 2012] Wei, T., Liang, X., He, Y., Zang, Y., Han, Z., Caramazza, A., and Bi, Y. (2012). Predicting Conceptual Processing Capacity from Spontaneous Neuronal Activity of the Left Middle Temporal Gyrus. *Journal of Neuroscience*, 32(2):481–489.

[Weissman et al., 2006] Weissman, D. H., Roberts, K. C., Visscher, K. M., and Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience*, 9(7):971–978.

[Weng et al., 2010] Weng, S.-J., Wiggins, J. L., Peltier, S. J., Carrasco, M., Risi, S., Lord, C., and Monk, C. S. (2010). Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain research*, 1313:202–14.

[Westlye et al., 2009] Westlye, L. T., Walhovd, K. B., Bjornerud, A., Due-Tonnessen, P., and Fjell, A. M. (2009). Error-related negativity is mediated by fractional anisotropy in the posterior cingulate gyrus - A study combining diffusion tensor imaging and electrophysiology in healthy adults. *Cerebral Cortex*, 19(2):293–304.

[Whitfield-Gabrieli and Ford, 2012] Whitfield-Gabrieli, S. and Ford, J. M. (2012). Default Mode Network Activity and Connectivity in Psychopathology. *Annual Review of Clinical Psychology*, 8(1):49–76.

[Whitfield-Gabrieli et al., 2009] Whitfield-Gabrieli, S., Thermenos, H. W., Milanovic, S., Tsuang, M. T., Faraone, S. V., McCarley, R. W., Shenton, M. E., Green, A. I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J. D. E., and Seidman, L. J. (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, 106(4):1279–84.

[Whitney et al., 2012] Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., and Jefferies, E. (2012). Executive Semantic Processing Is Underpinned by a Large-scale Neural Network: Revealing the Contribution of Left Prefrontal, Posterior Temporal, and Parietal Cortex to Controlled Retrieval and Selection Using TMS. *Journal of Cognitive Neuroscience*, 24(1):133–147.

[Winer and Schreiner, 2009] Winer, J. A. and Schreiner, C. E. (2009). *The Auditory Cortex*. Sinauer Associates.

[Winston et al., 2002] Winston, J., Strange, B., O'Doherty, J., and Dolan, R. (2002). Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nature Neuroscience*, 5(3):277–283.

[Wolf et al., 2008] Wolf, R. C., Sambataro, F., Vasic, N., Schönfeldt-Lecuona, C., Ecker, D., and Landwehrmeyer, B. (2008). Aberrant connectivity of lateral prefrontal networks in presymptomatic Huntington's disease. *Experimental Neurology*, 213(1):137–144.

[Wood et al., 2005] Wood, J. N., Romero, S. G., Knutson, K. M., and Grafman, J. (2005). Representation of attitudinal knowledge: Role of prefrontal cortex, amygdala and parahippocampal gyrus. In *Neuropsychologia*, volume 43, pages 249–259.

[Xia et al., 2013] Xia, M., Wang, J., and He, Y. (2013). BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. *PLoS ONE*, 8(7):e68910.

[Xu et al., 2014] Xu, K., Liu, H., Li, H., Tang, Y., Womer, F., Jiang, X., Chen, K., Zhou, Y., Jiang, W., Luo, X., Fan, G., and Wang, F. (2014). Amplitude of low-frequency fluctuations in bipolar disorder: A resting state fMRI study. *Journal of Affective Disorders*, 152-154(1):237–242.

[Yan et al., 2013] Yan, X., Brown, A. D., Lazar, M., Cressman, V. L., Henn-Haase, C., Neylan, T. C., Shalev, A., Wolkowitz, O. M., Hamilton, S. P., Yehuda, R., Sodickson, D. K., Weiner, M. W., and Marmar, C. R. (2013). Spontaneous brain activity in combat related PTSD.

[Yang et al., 2011] Yang, H., Wu, Q. Z., Guo, L. T., Li, Q. Q., Long, X. Y., Huang, X. Q., Chan, R. C. K., and Gong, Q. Y. (2011). Abnormal spontaneous brain activity in medication-naïve ADHD children: A resting state fMRI study. *Neuroscience Letters*, 502(2):89–93.

[Yang et al., 2015] Yang, J., Gates, K. M., Molenaar, P., and Li, P. (2015). Neural changes underlying successful second language word learning: An fMRI study. *Journal of Neurolinguistics*, 33:29–49.

[Yeo et al., 2011] Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zollei, L., Polimeni, J. R., Fischl, B., Liu, H., and Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*, 106(3):1125–1165.

[Ypma et al., 2016] Ypma, R. J., Moseley, R. L., Holt, R. J., Rughooputh, N., Floris, D. L., Chura, L. R., Spencer, M. D., Baron-Cohen, S., Suckling, J., Bullmore, E. T., and Rubinov, M. (2016). Default Mode Hypoconnectivity Underlies a Sex-Related Autism Spectrum. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 1(4):364–371.

[Zalesky et al., 2010] Zalesky, A., Fornito, A., and Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. *NeuroImage*, 53(4):1197–1207.

[Zang et al., 2004] Zang, Y., Jiang, T., Lu, Y., He, Y., and Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage*, 22(1):394–400.

[Zeidman et al., 2012] Zeidman, P., Mullally, S. L., Schwarzkopf, D. S., and Maguire, E. A. (2012). Exploring the parahippocampal cortex response to high and low spatial frequency spaces. *NeuroReport*, 23(8):503–507.

[Zhai et al., 2016] Zhai, H., Yu, Y., Zhang, W., Chen, G., and Jia, F. (2016). ACC and IPL networks in the perception of the faces of parents during selective tasks. *Brain Imaging and Behavior*, 10(4):1172–1183.

[Zhang et al., 2009a] Zhang, H., Tian, J., Liu, J., Li, J., and Lee, K. (2009a). Intrinsically organized network for face perception during the resting state. *Neuroscience Letters*, 454(1):1–5.

[Zhang et al., 2009b] Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Yang, Z., Liao, W., Chen, Z., Shi, J., and Liu, Y. (2009b). Impaired attention network in temporal lobe epilepsy: A resting FMRI study. *Neuroscience Letters*, 458(3):97–101.

[Zhu et al., 2008] Zhu, C. Z., Zang, Y. F., Cao, Q. J., Yan, C. G., He, Y., Jiang, T. Z., Sui, M. Q., and Wang, Y. F. (2008). Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder. *NeuroImage*, 40(1):110–120.

[Zink et al., 2008] Zink, C. F., Tong, Y., Chen, Q., Bassett, D. S., Stein, J. L., and Meyer-Lindenberg, A. (2008). Know Your Place: Neural Processing of Social Hierarchy in Humans. *Neuron*, 58(2):273–283.

[Zou et al., 2008] Zou, Q. H., Zhu, C. Z., Yang, Y., Zuo, X. N., Long, X. Y., Cao, Q. J., Wang, Y. F., and Zang, Y. F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: Fractional ALFF. *Journal of Neuroscience Methods*, 172(1):137–141.

[Zuo et al., 2010] Zuo, X. N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., Castellanos, F. X., Biswal, B. B., and Milham, M. P. (2010). The oscillating brain: Complex and reliable. *NeuroImage*, 49(2):1432–1445.